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Where is mania in the meta-structure of psychopathology?

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Abstract

Background. The nosology of mania has long been a conundrum. Prior studies have alternately concluded that it is an internalizing disorder, a thought disorder, or a unique condition. Unfortunately, nearly all existing studies assessed symptoms cross-sectionally. This is problematic for syndromes that follow a more episodic course, such as mania. Here, we test whether including a history of episodes, not simply current symptoms, can help resolve the placement of mania in the meta-structure of psychopathology.

Methods. First-admission patients with psychosis from the Suffolk County Mental Health Project (N = 337) were followed across 20 years. Internalizing, thought disorder, and mania symptoms were assessed at year 20, whereas corresponding episodes (i.e. depressive, psychotic, and manic) were assessed across three intervals spanning the previous 20 years. We tested five models to determine whether mania (current and past) loaded onto the internalizing factor, the thought disorder factor, or an independent factor. A final model was validated against established markers of bipolar disorder.

Results. For depression and psychosis, current and past markers were congruent in loading onto internalizing and thought disorder factors, respectively. However, current and past markers of mania diverged: current mania was most strongly related to the thought disorder dimension, whereas past mania formed an independent factor. Classic correlates of mania – including family history, genetic risk, and neuropsychological function – were associated only with the history of mania dimension.

Conclusions. Including illness course in structural models of psychopathology suggests that mania is distinguished from internalizing and thought disorder factors, whereas assessments of current symptoms place it with psychosis. These findings require independent validation, but if replicated, they would support a separate spectrum of mania defined by the occurrence of episodes across the lifetime.

Introduction

Elucidating the meta-structure of mental disorders – how psychopathology can be more parsimoniously organized into higher-order dimensions – remains ongoing. Proponents argue that meta-structure can help to resolve comorbidity and identify better phenotypic targets for studies of etiology, pathophysiology, or treatment response (e.g. Andrews et al., 2009; Jonas et al., 2024; Kotov et al., 2020, 2024; Krueger et al., 2021; Watson et al., 2022) and may match subjective experience (Ringwald et al., 2025), but others question evidence supporting this utility (e.g. First, 2009; Tyrer, 2018; Wittchen, Beesdo, & Gloster, 2009; Zimmerman, 2021) or propose other approaches that may provide more benefit (e.g. Cuthbert, 2022; Eaton et al., 2023; McGorry et al., 2025; Robinaugh, Hoekstra, Toner, & Borsboom, 2020). Despite the debate, contours of a higher-order meta-structure have been articulated and some of its major dimensions replicated (Kotov et al., 2022). Even with active work in this area, however, the placement of mania – the defining feature of bipolar I disorder – in the meta-structure of psychopathology remains unresolved.

Bipolar I disorder has similarities with both depressive and psychotic disorders in regard to etiology, biomarkers, and treatment response (Goldberg, Andrews, & Hobbs, 2009; Kotov et al., 2020; Watson et al., 2022) and could reasonably be placed in either chapter. In the last revision of the *Diagnostic and Statistical Manual* (DSM-5), bipolar disorders were given their own chapter, between that of depressive disorders and psychotic disorders, 'in recognition of their place as a bridge' between those two classes (Regier, Kuhl, & Kupfer, 2013). Quantitative models of psychopathology have also struggled with mania's placement. For example, the Hierarchical Taxonomy of Psychopathology (HiTOP; Kotov et al., 2017) organizes symptoms hierarchically

Table 1. Structural studies of mania

Publication	Sample	Phenotype	Placement of mania
Caspi et al. (2014)	Community	Past-year symptoms[a]	Thought disorder
Forbes et al. (2021)	Community/Clinical	Current symptoms	Thought disorder
Keyes et al. (2013)	Community	Lifetime diagnoses	Split
Kotov et al. (2011)	Clinical	Lifetime diagnoses	Thought disorder
Krabbendam et al. (2004)	Community	Current and lifetime symptoms	Independent factor
Levin-Aspenson, Khoo, and Kotelnikova (2019)	Community	Lifetime diagnoses	Thought disorder
Stanton et al. (2023)	Clinical panel	Current symptoms	Thought disorder
Wolf et al. (1988)	Clinical	Lifetime diagnoses	Internalizing
Wright et al. (2013)	Community	Lifetime symptoms	Internalizing

[a]Past-year symptoms were assessed at multiple points across early adulthood.

from narrow traits to at least six broader spectra (i.e. internalizing [emotional distress, fear], disinhibited externalizing [distractibility, risk taking], antagonistic externalizing [callousness, entitlement], thought disorder [unusual beliefs, perceptual disturbances], detachment [social withdrawal, inexpressivity], and somatoform [physical symptom preoccupation]). Mania's placement in this structure, however, has been unresolved and so remains provisional on both internalizing and thought disorder. Table 1 summarizes structural analyses that included indicators of both internalizing and thought disorder dimensions, and shows that mania has been variously located on the internalizing dimension (Wolf et al., 1988; Wright et al., 2013), the thought disorder dimension (Caspi et al., 2014; Forbes et al., 2021; Kotov et al., 2011; Levin-Aspenson, Khoo, & Kotelnikova, 2019), both simultaneously (Keyes et al., 2013), or on a separate factor entirely (Krabbendam et al., 2004; Stanton et al., 2023).

The mixed literature summarized above has left unclear the placement of mania in the meta-structure of psychopathology and speaks to the need for new methods to address the question (Jonas et al., 2024; Kotov et al., 2017, 2022). Importantly, evidence, to date, has been based almost entirely on cross-sectional studies, with information about the course of mania or past episodes absent from these models. This represents a major limitation because mania is distinguished from both depression and psychosis by its tendency to follow an episodic course often with complete symptom remission between episodes (Gignac, McGirr, Lam, & Yatham, 2015;Judd et al., 2002; Solomon et al., 2010). Among those with bipolar I disorder, symptoms of mania are present for only 2%–11% of the time (Judd et al., 2002; Solomon et al., 2010). By comparison, depression and psychosis-related conditions tend to be more stable over time (e.g. Kotov et al., 2020). For example, psychosis-related traits demonstrate remarkable 10-year stability (Hopwood et al., 2013), and schizophrenia remission and recovery rates over time are lower than those observed following a manic episode (e.g. AlAqeel & Margolese, 2012; Gignac, McGirr, Lam, & Yatham, 2015; Jaaskelainen et al., 2013). Depression and other internalizing conditions showed moderate to strong continuity across years of assessment (Lahey et al., 2014), and evidence from studies looking at the stability of underlying internalizing conditions related to depression and related disorders showed considerable stability in youth and middle age (Fergusson, Horwood, & Boden, 2006; Gustavson et al., 2020). Yet, despite differences in stability across time, virtually all structural studies, to date, are based on symptoms present only at the time of assessment, so the resulting structures may reflect persistent internalizing and thought disorder symptoms, rather than symptoms of mania that have remitted. Assessing the longitudinal course of symptoms may be essential for disentangling mania from more stable forms of psychopathology.

Moreover, very few studies of mania's placement in the meta-structure take the step of validating their final disposition. In other words, they consider only the co-occurrence of signs and symptoms using structural evidence, but not whether the structure aligns with other validators of pathophysiology, such as biomarkers or family history (cf. Forbes et al., 2024). The one exception found was that thought disorder, which included mania, was associated with a greater family history of depression and neuropsychological impairment (Caspi et al., 2014). In considering potential validators of any final structural model, one can draw upon a robust literature showing that bipolar disorder is distinguished from other serious mental illness by elevation on bipolar polygenic risk score (PRS), good premorbid adjustment, treatment with mood stabilizers, and relatively intact cognitive functioning (Carlson et al., 2012; Kotov et al., 2020; Watson et al., 2022). If mania is correctly situated within the meta-structure, the dimension on which it falls should be associated with these markers.

The aim of the present study was to evaluate how data on the course of mania – not just current symptoms – would affect the placement of mania in the meta-structure of psychopathology and whether the resulting model aligned with classic validators of bipolar disorder. Current symptoms of internalizing, thought disorder, and mania were assessed by interviewer ratings as part of a 20-year longitudinal study. Additionally, the course of core symptoms related to these three constructs (i.e. history of depressive, manic, and psychotic episodes) was also ascertained during interviews conducted across the 20 years. Based on prior research, it was hypothesized that current and past markers of depression and psychosis would cohere and load on separate internalizing and thought disorder dimensions, respectively (Kotov et al., 2017). We then tested whether mania best fit with internalizing, thought disorder, or its own independent spectrum, and whether adding information from course (i.e. past episodes) altered this placement. Finally, we validated the best resulting structure against known correlates of bipolar disorder, including genetic risk, good premorbid adjustment, treatment with mood stabilizers, and smaller neuropsychological impairments relative to other psychotic disorders (Carlson et al., 2012; Kotov et al., 2020; Watson et al., 2022).

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Methods

Sample

Data were drawn from the Suffolk County Mental Health Project, a longitudinal study of first-admission psychosis. Participants were recruited from all 12 inpatient psychiatric hospitals in Suffolk County, New York (response rate 72%), between 1989 and 1995 (Bromet et al., 1992). Eligibility criteria were residence in Suffolk County, first admission within the past 6 months, no apparent organic etiology for psychosis, ability to speak English, IQ >70, and age between 15 and 60 years. Written consent was obtained from all study participants, or from parents in the case of minors. The Stony Brook University Committee on Research Involving Human Subjects and the review boards of participating hospitals approved the protocol annually.

During the baseline wave, 628 participants met the inclusion criteria. Participants were reassessed 6 months, 24 months, 48 months, 10 years, and 20 years after first admission. As of the 20-year follow-up, 81 participants had died. Of the 547 surviving participants, 70 were lost to follow-up, 33 could not be reached for varying reasons (moved to another country, institutionalized, or too ill to consent), and 71 declined to be interviewed. The remaining 373 participated in the 20-year follow-up in some form, but only 337 of these cases completed the full 20-year measures and are the focus of the present analyses. Research diagnoses were made by the consensus of study psychiatrists at year 20 using all available longitudinal information, including results of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (Spitzer, Williams, Gibbon, & First, 1992) interviews with participants' significant others, medical records, and observations and behavioral ratings by master's-level interviewers. Diagnoses were made according to DSM-IV criteria, as previously described (Bromet et al., 2011). Table 2 reports the demographic characteristics of the sample, as well as diagnoses and descriptive statistics for symptoms. An analysis of attrition compared cases who participated in the 20-year assessment to surviving participants who did not. Participants were more likely to be Caucasian (81% vs. 69%) and have bipolar disorder (34% vs. 21%), but did not differ from non-participants in gender, age at psychosis onset, or age at the time of assessment (Supplementary Table 1).

Measures

Current symptoms

Master's-level mental health professionals made ratings of symptoms based on their interviews with the participant, interviews with significant others, and medical records. Symptoms were rated using the SCID (First & Gibbon, 2004), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), the Hamilton Depression Rating Scale (Williams, 1988), and the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978).

Internalizing/depressive symptoms were captured from two composite scales. The first was derived from nine current symptoms of depression assessed by the SCID (scores range 9–27), administered without skip-outs, and the second was a composite of the 21 symptoms assessed by the Hamilton Depression Rating Scale (range 0–63) (Kotov, Guey, Bromet, & Schwartz, 2010; Williams, 1988). Thought disorder symptoms were measured with the reality distortion and disorganization scales of SAPS developed previously (Kotov et al., 2016). Mania symptoms were captured through three subscales – activation, cognition, and agitation – derived from an exploratory factor analysis of the YMRS. The factor loading matrix is reported in Supplementary Table 2. All scales for current symptoms had acceptable internal reliability (i.e. Cronbach's alpha ≥ .67).

Table 2. Sample descriptive statistics

	Cases			
	N	%	Mean	SD
Gender				
Male	194	57.6%		
Female	143	42.4%		
Ethnicity				
Caucasian	272	80.7%		
African-American	39	11.6%		
Other	26	7.7%		
Age			48.4	9.2
SCID – Depression			12.0	3.7
HDRS – Depression			6.4	6.4
SAPS – Reality Dist.			3.2	6.3
SAPS – Disorg.			6.1	1.6
YMRS – Activation			0.6	1.6
YMRS – Cognition			2.7	3.4
YMRS – Agitation			0.3	0.8
Dep. Epi. BL–4Y	141	45.2%		
Dep. Epi. 4Y–10Y	84	27.4%		
Dep. Epi. 10Y–20Y	121	36.4%		
Psyc. Epi. 6mo–4Y	149	51.4%		
Psyc. Epi. 4Y–10Y	160	52.3%		
Psych. Epi. 10Y–20Y	178	53.5%		
Man. Epi. BL–4Y	131	42.1%		
Man. Epi. 4Y–10Y	38	13.7%		
Man. Epi. 10Y–20Y	30	10.0%		
Diagnosis				
SZ	168	49.9%		
BP	88	26.1%		
MDD	32	9.5%		
Other Psy	49	14.5%		

Note: 10Y, 10 years; 20Y, 20 years; 4Y, 4 years; 6mo, 6 months; BL, baseline; BP, bipolar disorder; Dep. Epi., Depressive Episode; HDRS, Hamilton Depression Rating Scale; Man. Epi., Mania Episode; MDD, major depression; Other Psy, other psychotic disorders; Psyc. Epi., Psychosis Episode; SA, schizoaffective disorder; SAPS, Scale for the Assessment of Positive Symptoms; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders; SIP, substance-induced psychosis; SZ, schizophrenia; YMRS, Young Mania Rating Scale.

Course of symptoms

A timeline of manic, depressive, and psychotic episodes was generated at three time points across the 20 years (i.e. 4-year, 10-year, or 20-year assessment). Assessments were conducted 6 months, 24 months, 48 months, 10 years, and 20 years after the baseline. These timelines were created based on data from clinical interviews, medical records, and interviews with significant others, with coders coding whether episodes had occurred in the preceding interval. Manic and depressive episodes were defined according to DSM-IV

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criteria for each, respectively. Psychotic episodes were defined as the presence of any threshold psychotic symptom assessed by SCID Module B. Psychosis was counted from month 6 on, but not before 6 months, as nearly everyone was in a psychotic episode at baseline. The episode timelines were coded dichotomously to indicate whether a manic, depressive, or psychotic episode occurred during the three intervals: early (baseline/6-month to 4-year), middle (4-year to 10-year), and late (10-year to 20-year). Frequencies and descriptive statistics for all symptom marker variables are reported in Table 2.

Validators

Family history of bipolar disorder and family history of depression

Family history was assessed based on interviews with family members, the participant's report, and medical records. Both were operationalized as dichotomous variables, rated 1 if any of the participant's first-degree relatives had been diagnosed with bipolar disorder or depression, and 0 otherwise.

Polygenic risk scores

DNA was collected from 249 participants as part of the Genomic Psychiatry Cohort (Pato et al., 2013). DNA was extracted from peripheral lymphocytes and genotyped using the Illumina PsychArray-8 platform containing 571,054 markers. For details of quality control, see Jonas et al. (2019).

Bipolar and schizophrenia PRSs were calculated for each participant based on the summary statistics from the most recent Psychiatric Genomics Consortium (PGC) genome-wide association study (GWAS) results (available at http://ldsc.broadinstitute.org/ldhub/; Mullins et al., 2021; Trubetskoy et al., 2022). single nucleotide polymorphisms (SNPs) were clumped to a more significant SNP if they were in linkage disequilibrium (LD) ($r^2 > 0.10$) within a 500 kb window. PRS calculation was carried out in PRSice (Eusden, Lewis, & O'Reilly, 2015). PRS used all available SNPs and weights *a priori* to minimize multiple testing (i.e. a *p*-value threshold of 1). Results at other thresholds were similar. Analyses of PRS were completed in the subset of European ancestry participants ($N = 201$). European ancestry was defined as those participants determined to be ≥80% European ancestry according to ADMIXTURE analyses (Alexander, Novembre, & Lange, 2009), and within three standard deviations of the mean for the first three principal components of population stratification (Privé et al., 2020). All analyses were covaried on the first 10 principal components of population stratification in order to control for confounding due to ancestry (Price et al., 2006).

Premorbid adjustment

Premorbid psychosocial functioning was assessed using an interview based on the Premorbid Adjustment Scale (PAS; Cannon-Spoor, Potkin, & Wyatt, 1982; Rabinowitz, Levine, Brill, & Bromet, 2007), which was administered to participants and significant others at the 6-month follow-up. PAS ratings were based on these interviews and school records. Rating periods covered childhood (up to age 11), early adolescence (ages 12–15), and late adolescence (ages 16–18). The last available PAS composite prior to psychosis onset was used. The PAS consists of five domains (sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and social–sexual relationships) rated on a 7-point scale (scores range from 0 to 6, with 0 representing good functioning). Composite scores were calculated as the mean of the five PAS items, with scores reversed so that higher numbers indicate better functioning.

Medication history

Medication data were documented based on self-report, pill bottles and medication lists brought to follow-up appointments, and medical records. Lifetime history of treatment with mood stabilizers was operationalized as the sum of intervals during which the participant took this class of medication, weighted by the length of the interval.

Neuropsychological performance

Cognitive tests performed at the 20-year follow-up included performance on the word reading subtest of the WRAT-3 (a proxy for premorbid academic achievement; Wilkinson, 1993), Trails B (Reitan, 1955), and the Controlled Oral Word Association Test (Bechtoldt, Benton, & Fogel, 1962). These tests were selected from a larger neuropsychological battery because they distinguish bipolar disorder from first-episode schizophrenia (Bora & Pantelis, 2015).

Supplementary Table 3 reports the descriptive statistics for all validators.

Analyses

Code for all analyses is available from the corresponding author on request. Parallel analysis was performed in R using the 'paran' package (Dinno, 2018; R Core Team, 2021). All latent variable models were estimated in Mplus, version 7 (Muthen & Muthen, 2007), using maximum likelihood estimation with robust standard errors. This estimator uses all available data, including partial cases, and is robust to non-normality of the indicators. Model comparisons were evaluated based on the Bayesian Information Criterion, as well as the interpretability of factors (Clark & Watson, 1995). Latent variable models of symptoms were estimated using confirmatory factor analysis. Validators were regressed on the latent factors in structural equation models.

Results

Mania in the meta-structure

The first model (Model A or the internalizing model) specified that all mania markers (i.e. current symptoms and past episodes) load with the internalizing dimension. The second model (Model B or the thought disorder model) specified that all mania markers load with the thought disorder dimension. The third model (Model C or independent mania model) specified a third independent dimension separate from internalizing and thought disorder factors and composed of both current and past episode mania markers.

We next tested two split models based on the hypothesis that current and past markers of mania would capture different information. Therefore, a separate mania dimension composed of only past markers would form a factor split off from current symptoms. One model had current symptoms load onto internalizing (Model D1), and the other had current symptoms load onto thought disorder (Model D2).

Table 3 reports the results of these five models, and Supplementary Table 4 reports their fit indices. The internalizing model (Model A) had the worst fit, with current mania markers loading only weakly and past mania loading not at all or negatively onto the internalizing dimension. The thought disorder model (Model B) had improved fit over Model A. Current mania markers had loadings on this dimension (i.e. all loadings >.35), but past mania episodes failed to load onto this factor (i.e. all loadings <.03).

The independent mania model (Model C) showed the best relative fit of all models. However, this model had two major

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Table 3. Model factor loadings and correlations

	Model A (internalizing)		Model B (thought disorder)		Model C (independent mania)			Model D1 (split with internalizing)			FINAL MODEL Model D2 (split with thought disorder)		
	INT	TD	INT	TD	INT	TD	MAN	INT	TD	MAN HX	INT	TD	MAN HX
SCID – Depression	0.73		0.87		0.98			0.73			0.87		
HDRS – Depression	0.70		0.76		0.71			0.90			0.76		
Dep. Epi. BL–4Y	0.16		0.22		0.22			0.16			0.22		
Dep. Epi. 4Y–10Y	0.26		0.31		0.28			0.26			0.31		
Dep. Epi. 10Y–20Y	0.38		0.53		0.57			0.38			0.54		
SAPS – Reality Dist.		0.86		0.54		0.55			0.86			0.54	
SAPS – Disorg.		0.35		0.73		0.67			0.35			0.73	
Psyc. Epi. 6mo–4Y		0.54		0.41		0.41			0.54			0.41	
Psyc. Epi. 4Y–10Y		0.80		0.59		0.60			0.80			0.59	
Psyc. Epi. 10Y–20Y		0.98		0.75		0.77			0.98			0.75	
YMRS – Activation	0.09			0.40			0.36	0.10				0.40	
YMRS – Cognition	0.39			0.92			0.99	0.39				0.92	
YMRS – Agitation	0.21			0.35			0.31	0.21				0.36	
Man. Epi. BL–4Y	−0.15			−0.05			−0.05			0.54			0.53
Man. Epi. 4Y–10Y	−0.01			0.02			−0.04			0.97			0.97
Man. Epi. 10Y–20Y	0.07			−0.15			−0.23			0.79			0.80
Internalizing	1.00		1.00		1.00			1.00			1.00		
Thought disorder	0.39	1.00	0.20	1.00	.018	1.00		.39	1.00		0.20	1.00	
Mania or mania HX	–	–	–	–	0.07	0.89	1.00	−.05	−.04	1.00	0.04	−0.04	1.00

Note: Scales assessing mania are bolded. 10Y, 10 years; 20Y, 20 years; 4Y, 4 years; 6mo, 6 months; BL, baseline; Dep. Epi., Depressive Episode; HDRS, Hamilton Depression Rating Scale; INT, internalizing; MAN HX, history of mania; MAN, mania; Man. Epi., Mania Episode; Psyc. Epi., Psychosis Episode; SAPS, Scale for the Assessment of Positive Symptoms; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders; TD, thought disorder; YMRS, Young Mania Rating Scale.

limitations that led to its rejection. First, there was an excessively high overlap between the thought disorder dimension and the independent mania dimension (i.e. r = .89). This extremely high correlation indicated that these two factors are not distinct. Second, past mania markers had negative loadings onto this dimension, suggesting that the course of mania and current mania do not fit on the same factor.

For both reasons, Models D1 and D2 (the split model) were run. Here, current mania symptom markers were allowed to load with either the internalizing (D1) or the thought disorder (D2) dimension, but past mania markers formed an independent mania history factor.

Model D2 (current mania loading onto Thought Disorder) showed a better fit than D1 (mania on Internalizing) and was selected as the final model. It also had, by far, the lowest chi-square value of all the models analyzed (Supplementary Table 4). Most importantly, this solution resolved the limitations of Model C: factor dimensions were all largely independent in Model D2, with good discrimination from one another (i.e. r's ≤ .20), and all mania markers loaded onto their respective factors (i.e. all loadings >.35). Moreover, Model D2 showed superior fit to Models A and B. - Figure 1 displays Model D2.

Validation

Validators were regressed on the three latent factors simultaneously of the final model selected (i.e. Model D2 or the split model). The results of these analyses are reported in Table 4 and supported the selection of Model D2 as the final model. Course markers reflecting a past history of mania factor showed the most robust association with mania-related validators. This factor was associated with family history of bipolar disorder, family history of depression, and higher bipolar PRSs. It was also associated with better premorbid adjustment and better cognitive function. This factor was also associated with mood stabilizer treatment more strongly than the other factors.

Internalizing was associated with a greater family history of bipolar disorder and depression, but not other mania-related validators. Thought disorder was linked to greater genetic liability for schizophrenia, worse premorbid function, worse cognitive performance (i.e. higher scores on Trials B), and less treatment with mood stabilizers. This dimension included current mania symptoms, but its external correlates were largely opposite of what's expected for mania. Overall, validation largely supported the final model selection that had past mania markers independent from thought disorder and internalizing factors.

Discussion

In a study of 337 individuals with psychotic disorders, current and past symptoms of mania diverged in their placement in the meta-structure of psychopathology. Current symptoms aligned with the thought spectrum, but markers of past mania formed their own,

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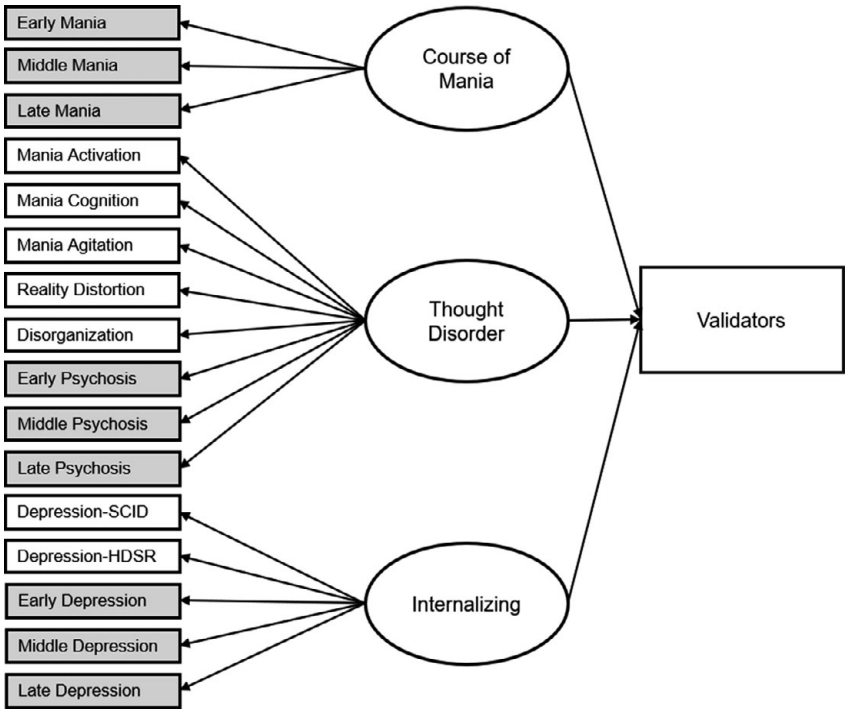

Figure 1. Final structural model (D2) displaying placement of mania markers.
Note: Course variables are filled in gray. All factors are correlated (not shown). Table 3 reports scale loadings and factor correlations. Table 4 reports the regression of validators on the three latent factors.

Table 4. Regression of bipolar disorder validators on the final model's three latent factors

	Internalizing		Thought disorder		History of mania	
Validator	β	95% CI	β	95% CI	β	95% CI
Family history of bipolar disorders	**0.18**	**[0.04, 0.32]**	−0.05	[−0.13, 0.03]	**0.19**	**[0.08, 0.30]**
Family history of depression	**0.11**	**[0.21, 0.31]**	−0.05	[−0.15, 0.05]	**0.14**	**[0.02, 0.26]**
BP PRS	−0.03	[−0.14, 0.09]	−0.04	[−0.17, 0.09]	**0.34**	**[0.20, 0.49]**
SZ PRS	−0.08	[−0.26, 0.11]	**0.21**	**[0.08, 0.35]**	−0.06	[−0.24, 0.12]
Premorbid adjustment[a]	−0.09	[−0.21, 0.03]	**−0.25**	**[−0.36, −0.14]**	**0.42**	**[0.30, 0.54]**
Lifetime treatment with mood stabilizers	0.09	[−0.04, 0.22]	**−0.16**	**[−0.25, −0.07]**	**0.50**	**[0.40, 0.61]**
Word reading	0.05	[−0.08, 0.18]	−0.09	[−0.23, 0.04]	**0.48**	**[0.35, 0.61]**
Trails B[a]	0.05	[−0.19, 0.08]	**−0.18**	**[0.05, 0.31]**	**0.48**	**[−0.61, −0.35]**
COWAT	0.04	[−0.07, 0.16]	−0.07	[−0.18, 0.06]	**0.39**	**[0.23, 0.54]**

Note: Statistically significant associations are bolded. BP PRS, bipolar polygenic risk score; COWAT, Controlled Oral Word Association Test.
[a]Premorbid adjustment and Trails B scores were reversed such that higher scores indicate better functioning.

independent spectrum. Most critically, this dimension reflecting course (i.e. past episodes of mania) was the only one closely related to known correlates of bipolar I disorder – such as genetic risk, good premorbid functioning, and treatment with mood stabilizers. Three overarching conclusions may be drawn from this study. First, cross-sectional assessment of symptoms represents a major limitation of structural research on mania's placement in quantitative nosology. This finding is not surprising, given that cross-sectional assessment methods are more likely to miss clinical phenomena like mania that are better identified through longitudinal assessment. Yet it is nevertheless important for models like HiTOP to keep in mind, given that they may misrepresent the meta-structure whenever they rely solely on cross-sectional evidence. More generally, episodicity may represent an independent feature for some forms of psychopathology, and so may need to be explicitly integrated into structural models. Second, evidence from this study suggests that mania's placement in the meta-structure of psychopathology is in its own spectrum, independent from either the internalizing or thought disorder dimensions. Third, current symptoms of mania per se were not validated in the present study as related to key markers of bipolar disorder and instead captured the thought disorder spectrum.

Foremost, results from this study underscore how illness course is an essential feature of mania that may be independent from

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current symptoms. Our findings are consistent with the long-standing view that assessing illness course is critical to the assessment of bipolar disorder (Frank, Nimgaonkar, Phillips, & Kupfer, 2015) and align with a long-standing validator for psychiatric disorders within traditional nosology (Kraepelin, 1899; Robins & Guzé, 1970). Illness course has been missing from most past structural work attempting to adjudicate mania's placement in the meta-structure of psychopathology, and may be one reason for conflicting findings on whether mania is better conceptualized as part of internalizing, thought disorder, or its own dimension (Kotov et al., 2017, 2022). Our results underscore that better incorporation of course features may be necessary for quantitative models of nosology, such as HiTOP. The extent of this need beyond mania remains an open question since course is not likely to be universally critical for placing psychopathology within a meta-structure. For example, internalizing, thought disorder, and externalizing dimensions exhibit high rank-order stability over many years (Eaton, Krueger, & Oltmanns, 2011; Jonas et al., 2024; Krueger, Caspi, Moffitt, & Silva, 1998) and so are less likely to show divergence between current and past symptoms. Indeed, in the present study, current and past symptoms were placed on the same spectrum for internalizing and thought disorder. Mania likely showed divergence because it is considerably less stable over time.

Beyond implications with respect to course, the present study found that current symptoms of mania not only failed to load with past episodes, but also loaded onto a factor that was not associated with traditional validators of bipolar disorder. For example, the factor they loaded onto was much more strongly related to genetic risk for schizophrenia than for bipolar disorder. Part of this finding may be related to measurement. Our results are consistent with previous research findings that interviewer-rated mania is often linked to thought disorder (Caspi et al., 2014; Kotov et al., 2011). However, an important factor here is that symptoms of mania overlap with symptoms of schizophrenia, so that differential diagnosis is often based on course and outcome rather than presenting symptoms. Notably, genetic risk for bipolar disorder has been associated with the number of hospitalizations over the course of illness (Kalman et al., 2022), but not cross-sectional phenotypes reflecting clinical profiles (Dwyer et al., 2020) nor the distinction between affective and non-affective psychosis (Rodriguez et al., 2022). In short, when it comes to mania, the content of symptoms may be less important than their course over time.

Research and clinical relevance of present findings, and meta-structure broadly, requires further investigation (e.g. Tyrer, 2018; Zimmerman, 2021). However, if replicated, findings carry potential implications. With regard to research, dimensional studies of psychotic disorders have focused on symptom severity and may overlook heterogeneity related to characteristics of illness course. Indeed, patients with the same psychotic symptom profiles may either remit quickly or suffer from a protracted illness that does not fully resolve. Adding the mania history factor to the study design can reduce this heterogeneity, allowing studies to disentangle the effects of chronicity and symptom severity. This is relevant for research ranging from etiology to treatment response. For example, we found that mania history and mania severity (thought disorder) dimensions have very different – and sometimes opposite – associations with genetic vulnerabilities, cognitive functioning, and utilization of mood stabilizers. With regard to clinical relevance, longitudinal course has long been recognized as essential for the identification of bipolar disorder in traditional nosologies, and the present study extends this to suggest that quantitative classifications likewise need to capture mania history when conducting assessments. With regard to prognosis, mania history factor may be informative, as given the same severity of thought disorder symptoms, patients elevated on this history factor may be more likely to follow an episodic course, whereas patients without this elevation may be more chronic. We do not have data to test this possibility directly, and further research is needed to evaluate it.

Despite the importance of our findings for structural models of psychopathology and its possible research and clinical relevance, important limitations need to be acknowledged. People with bipolar I disorder who were never hospitalized were not included in this study, nor were those who did not experience at least some psychotic symptoms. An estimated 63% of manic episodes require hospitalization (de Zelicourt et al., 2003), and psychosis is observed in 58% (Goodwin & Jamison, 2007), suggesting that our sample is reasonably representative of bipolar I disorder. Nevertheless, the sample reflects more severe cases, so it will be important to replicate these findings among individuals who have not been hospitalized or experienced psychosis. Moreover, the present study was confined only to understanding mania's placement relative to internalizing and thought disorder spectra. This focus was motivated by the existing literature, as previous structural studies placed mania only in these two spectra. It will nevertheless be necessary and useful to examine mania in the context of all six HiTOP spectra, for example. The study also still mostly relied on cross-sectional assessments (albeit done repeatedly over time) and did not have a robust set of validators, such as a functional recovery or quality of life. As such, results should be considered preliminary until a prospective design with more robust validators can be used to validate this structure. In addition, assessment relied on a specific clinical interview, and although this measure is an established standard in bipolar disorder research (Young, Biggs, Ziegler, & Meyer, 1978), it will be important to confirm results with broader instruments. Additionally, this study was limited by attrition over follow-ups, and, like other studies of this kind, the point prevalence of mania was low. Both weaknesses were ameliorated by the lengthy follow-up and thorough phenotyping, which allowed for a rigorous assessment of premorbid characteristics, course, and treatment history. Finally, the overarching aim of the study was to understand mania's placement in the meta-structure of psychopathology; however, validating this overarching structure and its clinical utility will require considerably more work, with no definitive evidence yet that this will lead to better care for individual patients (cf. First, 2009; Tyrer, 2018; Wittchen, Beesdo, & Gloster, 2009; Zimmerman, 2021).

Conclusions

While current symptoms of mania overlapped with thought disorder psychopathology in the present study, the course of mania formed a distinct spectrum, which was not the case for past episodes related to thought disorder or internalizing. The dimension based on course was related to known correlates of bipolar disorder, including family history, genetic risk, and relatively preserved cognitive function, supporting the importance of distinguishing the course of mania from thought disorder and internalizing. If replicated, these results would support the addition of an independent mania spectrum to the HiTOP model. Incorporating course features is a necessary step for refining models of psychopathology.

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Data availability statement. Genotype data are available through dbGap (Accession no. phs001020.v2.p1). The phenotypic data that support the findings of this study are available from the corresponding author upon request.

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