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Identifying the bridge between depression and mania: A machine learning and network approach to bipolar disorder

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Abstract

Objectives: Although the cyclic nature of bipolarity is almost by definition a network system, no research to date has attempted to scrutinize the relationship of the two bipolar poles using network psychometrics. We used state-of-the-art network and machine learning methodologies to identify symptoms, as well as relations thereof, that bridge depression and mania.

Methods: Observational study that used mental health data (12 symptoms for depression and 12 for mania) from a large, representative Canadian sample (the Canadian Community Health Survey of 2002). Complete data ($N = 36{,}557$; 54.6% female) were analysed using network psychometrics, in conjunction with a random forest algorithm, to examine the bidirectional interplay of depressive and manic symptoms.

Results: Centrality analyses pointed to symptoms relating to emotionality and hyperactivity as being the most central aspects of depression and mania, respectively. The two syndromes were spatially segregated in the bipolar model and four symptoms appeared crucial in bridging them: *sleep disturbances (insomnia and hypersomnia)*, *anhedonia*, *suicidal ideation*, and *impulsivity*. Our machine learning algorithm validated the clinical utility of central and bridge symptoms (in the prediction of lifetime episodes of mania and depression), and suggested that centrality, but not bridge, metrics map almost perfectly onto a data-driven measure of diagnostic utility.

Conclusions: Our results replicate key findings from past network studies on bipolar disorder, but also extend them by highlighting symptoms that bridge the two bipolar poles, while also demonstrating their clinical utility. If replicated, these endophenotypes could prove fruitful targets for prevention/intervention strategies for bipolar disorders.

KEYWORDS
bipolarity, depression and mania, epidemiology, machine learning, network psychometrics

1 | INTRODUCTION

Manic-depressive illness (or, simply, bipolar disorder) is a severe and chronic mental disorder, characterized by two maladaptive states, depression and mania, that recur in a cyclic manner.[1] Clinical accounts of depression and mania are as old as medicine itself, and have been presented throughout history with strikingly unvarying descriptions.[2] Despite their definitional consistency, however, the boundaries that distinguish depression and mania, as well as the mechanisms that underlie their transitional nature, remain elusive. In this paper, we employ network and machine learning methods to map the statistical architecture of the two bipolar poles, hoping to reveal symptoms that link their boundaries, as well as clinically notable ways by which they do so.

Although much research exists on the psychopathology of depression, less attention has been paid to mania. Nonetheless, existing evidence has converged on a model whereby mania and depression are separate factors and not mere opposites of the same dimension.[3] Indeed, some studies have suggested that abnormal reward sensitivity processes may underpin mania, triggering it in response to rewarding events independent of depressive feelings.[4,5] Yet other studies have pointed to mania arising as a dysfunctional coping mechanism to battle feelings of depression.[6] Whether depression and mania are completely independent, however, is as of yet unknown. Thus far, psychological research has been modeling these constructs at the macroscopic level (with factor analysis), thereby obscuring the lower-level interactions among their symptoms.[1,3] Gaining insight into how individual depressive and manic symptoms interact can not only enhance the state of current interventions (by elucidating important symptom-level mechanisms), but can also inform neurobiological investigations (by revealing promising endophenotypes that are crucial to the development and maintenance of bipolar disorder).[7]

Psychometric network models enable these ends to be addressed. These models contrast with traditional latent variable ones (which view mental disorders as latent maladies that cause their respective symptomatologies), by positing that mental disorders arise from the causal relations among their symptoms.[8] In this sense, the activation of one symptom (for instance, insomnia) could lead to the activation of another (i.e., fatigue), and another (i.e., low mood), and so on, until sufficient symptoms are present to crystalize into a particular syndrome.[9,10] Statistical tools allow for these covariation patterns to be displayed in network graphs, wherein nodes (circles) represent symptoms and the edges (links) that connect them represent statistical associations.[11] By modeling psychopathology this way, important features of the symptom architecture can be revealed. For example, 'central' (or highly interconnected) symptoms, and clinically important pathways thereof, can be illuminated. Moreover, symptoms which 'bridge' different syndromes, and thereby contribute to comorbidity, can also be revealed.[12] Assuming reliable estimation, these centrality metrics were shown to be clinically useful, for instance, by exhibiting prognostic[13] or even diagnostic[14] capabilities.

Although some of these network tools have been applied to the study of depression[10,15] and mania,[16–18] less attention has been paid on their intersection (bipolar disorder). Previous network studies on bipolar disorder have focused on time-lagged relations of its symptoms,[19] comparison of its network structure between unipolar and bipolar patients,[20–23] and analyses on other related endophenotypes in bipolar patients, such as cognitive skills.[21] To our knowledge, only one study so far attempted to (indirectly) address the relationship between depression and mania via network analysis. This study, by Weintraub and colleagues,[24] was among the first to apply network psychometrics to bipolar symptomatology, focusing on central symptoms within a sample of treatment-seeking adolescents. However, this study had at least three limitations. First and foremost, recent tools that allow for quantifying the extent to which symptoms bridge different syndromes (in this case, the two bipolar poles) were not available at the time of their publication. Second, the study's low sample size reduced its statistical power, which may have led to the omission of true relations (i.e., false negatives) that bridge depression and mania. A final limitation, which applies to related studies, concerns the estimation of symptom networks in clinical populations. In particular, network structures from clinical populations (particularly the more severe ones) can bias the relations among symptoms (known as Berkson's bias).[25] To understand the symptoms that contribute to bipolarity, replication of bipolar symptom networks is necessitated in the general population.

In this study, we aim to address these limitations by specifically scrutinizing the relation between mania and depression in a large, epidemiological sample. Leveraging our large sample size via recent machine learning methods, we aim to estimate the statistical structure of bipolar symptomatology, model it as a network system, and identify predictive paths between the two bipolar poles. A secondary aim was to estimate the centrality of the bipolar model, as well as its two syndromes, and examine the degree of converge between our findings and those derived in clinical populations. Finally, moving beyond existing exploratory network research, we sought to examine whether our centrality metrics hold diagnostic utility, using state-of-the-art machine learning methodologies.

2 | METHOD

2.1 | Sample

The data for this study were acquired from the Mental Health and Well-Being (82-617-XIE) component of the Canadian Community Health Survey (CCHS), which was conducted in 2002 by Statistics Canada (see https://www150.statcan.gc.ca/n1/en/catalogue/82C0026). A multi-stage stratified cluster design was used to sample private dwellings, from which participants were recruited. Most of the interviews (86%) were conducted in person; the rest over telephone. Of those contacted, 77% responded, yielding a final sample size of 36,984 individuals aged 15 years or older. Our data were weighted in order to be representative of the household

population in the ten provinces of Canada at the time of the survey in 2002.

2.2 | Measurement instruments

The CCHS employed the World Health Organisation (WHO) World Mental Health version 2000 of the Composite International Diagnostic Interview[26] to collect information on lifetime and past 12-month prevalence of various mental illnesses, as well as determinants and other correlates of these illnesses. In this study, we used 24 symptoms (see Table 2), twelve for each syndrome (depression and mania), all of which were measured in a binary fashion. Diagnostic measures of lifetime episodes of mania and depression were further used. Table S1 outlines our clinical reasoning for including/excluding particular psychopathology symptoms in/from our networks. Briefly put, we aimed to include symptoms that are essential for a formal diagnosis of either syndrome and exclude those which exhibited statistical (e.g., collinearity) or theoretical (e.g., ontological similarity) issues.

2.3 | Statistical analyses

Data analysis was conducted using the statistical software R, version 4.1.2. In particular, the R packages *mgm*,[27] *qgraph*,[28] *igraph*,[29] *networktools*,[30] and *bootnet*[31] were used for the estimation and inferential analysis of our network models; the R package caret[32] was used for machine learning. Frequency statistics were used to characterize our cohort (Table 1), and estimate rates of symptom endorsement (Table 2). Listwise deletion was employed to handle missing values.

2.3.1 | Network estimation and visualization

To model conditional dependencies among symptoms, the Ising model was used. The Ising model has its origins in the field of statistical mechanics, wherein it was employed to model atomic spins that could either be upward {1} or downward {−1}.[33] Similarly, psychopathology symptoms, which could either be present {1} or absent {0}, can be modelled.[34] To construct our Ising models, we employed the *eLasso* estimation approach, which makes use of iterative *l*1 regularized logistic regressions to estimate pairwise relations among symptoms.[35] To select the final intra-syndromic models (depression and mania ones), we chose to reduce the Extended Bayesian Information Criterion (EBIC; $\gamma = 0.50$), as this approach accommodates our wish for *specificity* by ensuring sparser network structures (and so, lower likelihoods of Type I errors).[11,36,37] In contrast, to create the inter-syndromic (i.e., bipolar) model, we wished to balance *specificity* and *sensitivity* (as we were interested to reveal the most robust pathways between depression and mania); therefore, we employed a novel machine-learning estimation technique, namely, *k-fold cross-validation*. Using 6-fold cross-validation, we trained our Ising model in 5-folds, then tested its performance in the remaining fold, and repeated this procedure 100 times. To ensure robustness, we retained the edge-weights that were present at least 95% of the times across the testing sessions (see Supplement III for details).

Our statistical models were visualized as networks through the use of the Fruchterman–Reingold algorithm, which positions strongly connected nodes (symptoms) at the centre of the graph and weakly connected ones at its periphery.[38] In our network figures, blue and red edges denoted positive and negative conditional relations, respectively. Pie charts around nodes were also employed to denote the amount of explained variation within each symptom.[39]

TABLE 1 Demographic characteristics of Canadian cohort.

	Total ($N = 36,557$)[a]
Depressive episode	
Present	4601 (12.6%)
Absent	31,956 (87.4%)
Manic Episode	
Present	935 (2.6%)
Absent	35,622 (97.4%)
Age	
15 to 29	8160 (22.3%)
30–44	10,171 (27.8%)
45+	18,226 (49.9%)
Sex	
Male	16,603 (45.4%)
Female	19,954 (54.6%)
Marital status	
Single/Separated/Divorced/Widowed	17,516 (47.9%)
Married/Living with partner	19,000 (52.0%)
Missing values	41 (0.1%)
Educational level	
Less than high school graduation	10,450 (28.6%)
High school graduation	6435 (17.6%)
Some post-secondary	3012 (8.2%)
Post-secondary graduation	16,442 (45.0%)
Missing values	218 (0.6%)

[a]Excludes participants with missing values in symptom variables.

2.3.2 | Network inference

A number of inferential analyses were conducted to infer certain local and global properties of our networks. First, the expected influence (EI) centrality metric was estimated to identify the most central symptoms in all networks. The EI metric equals the sum of edge-weights linked to a given node and thereby allows us to quantify how strongly interconnected each symptom is in the networks.[40,41] Second, the *spinglass*[42] and *walktrap*[43] community-detection algorithms were employed to explore the factor (or community) structure

TABLE 2 Symptom endorsement rates in participants with complete data ($N = 36,557$).

Item label	Item description	*N* endorsement (Frequency %)[a]
D1	Sad, empty, or depressed	4813 (13%)
D2	Felt hopeless about the future	3274 (9%)
D3	Lost interest in all things	4167 (11%)
D4	Slept more than usual (hypersomnia)	588 (2%)
D5	Felt tired/low in energy	4367 (12%)
D6	Talked/moved more slowly than normal	2798 (8%)
D7	Trouble concentrating	4265 (11%)
D8	Unable to make up my mind	3509 (10%)
D9	Felt totally worthless	2218 (6%)
D10	Felt guilty nearly everyday	3527 (10%)
D11	Was often in tears	2663 (7%)
D12	It would be better if I were dead	2386 (6%)
M1	Irritable during manic episode	889 (2%)
M2	Became restless/fidgety	1944 (5%)
M3	Became overly friendly	1571 (4%)
M4	Slept far less than usual and was not tired	2082 (6%)
M5	Became more interested in sex than usual	706 (2%)
M6	Talked a lot more than usual	1931 (5%)
M7	Thoughts jumped from one thing to another	2396 (7%)
M8	Behaved in a way that was inappropriate	1618 (4%)
M9	Spend much more money than usual	1028 (3%)
M10	Did risky things for pleasure	1159 (3%)
M11	Had greatly exaggerated self-confidence	1059 (3%)
M12	Believed that I was someone else	177 (1%)

[a]Percentages were rounded to the nearest integer.

of the bipolar network. This was a crucial preliminary step to ensure that the statistical structure of the bipolar network model was two-dimensional and reflective of the depressive and manic syndromes. Third, assuming such a two-dimensional structure, the bridge expected influence (BEI) metric was calculated to identify symptoms that 'bridge' depression and mania.[44] The BEI equals the sum of (raw) edge-weights that link a node from one community (mania) to the nodes of another community (depression), and thereby allows us to quantify how 'influential' symptoms are in linking the two bipolar poles. Finally, the shortest paths between the two bipolar poles were highlighted in a separate graph, using Dijkstra's algorithm.[45] The shortest paths (between two given nodes) are those that yield the minimum conditional prediction error between them, and could prove fruitful in highlighting the most robust (i.e., shortest) ways by which symptoms from the manic and depressive communities are connected.[46]

2.3.3 | Machine learning

Random forest is a tree-based algorithm that allows for the ensemble of 'random' decision trees (which are based not only on random samples, but also selection of variables) for the prediction (here, classification) of an outcome. Our outcomes here were lifetime episodes of either mania or depression (both binary). We chose this machine learning approach for classifying whether someone has experienced depression or mania, as it requires minimal parameter tuning, as well as because, unlike other methods, it allows for estimates of predictor importance (that is, how important each predictor is during the classification process). Our variable importance measure was calculated as the mean decrease in model accuracy (MDA) during permutation. MDA was operationalized here as a measure of diagnostic utility, since a large MDA value for a particular symptom is indicative of a loss in classification power, when that symptom is excluded from the model. To prevent overfitting, we trained our algorithm on a randomly selected training sample (80%), and tested its predictive utility in a hold-out (testing) sample (20% of the data). For the training procedure, we made use of repeated k-fold cross-validation; in particular, 10 repetitions of 10-fold cross-validation (for a total of 100 trees).

2.3.4 | Robustness checks

In light of recent concerns regarding replicability of psychopathology networks,[37] we employed three robustness checks. First,

state-of-the-art bootstrapping methodologies (namely, the case-dropping and non-parametric ones) were used to scrutinize the stability of our centrality indices and replicability of edge-weight parameters (for the mania and depression networks).[36] Second, the robustness of the bipolar network model was indirectly examined via its estimation (cross-validation) procedure, through which the most replicable edge-weights were screened (that is, those with >95% replicability). Finally, logistic regression models were used (as a sensitivity check) to examine their degree of convergence with the machine-learning results.

3 | RESULTS

Table 1 outlines the demographic characteristics of our Canadian representative sample. Of the 36,557 participants (19,954; 54.6% female) with complete data, 12.6% and 2.6% experienced lifetime episodes of depression and mania, respectively. No statistically significant differences were found between the excluded participants and the included ones, in neither symptoms nor demographic characteristics. Most participants (49.9%) aged 45 years or older, were married or lived with a partner (52%), and had achieved at least post-secondary education (45%). From Table 2, it is evident that the most endorsed symptoms were depressive in nature, ranging from 6% for suicidal ideation to as high as 12%–13% for emotional and physical symptoms. For manic symptoms, endorsement rates were lower, ranging from 1% for delusional ideation (thinking I was someone else) to 8% for physical symptoms. Additional descriptions of the current dataset are beyond the scope of this study, but can be found elsewhere.[47]

3.1 | Depression and mania networks

Figure 1 displays the depression and mania Ising networks, as well as their centrality plots. Of the 66 possible edge parameters, 55 were identified in each network. The network estimation was deemed accurate, given the non-overlapping 95% CIs of the edge weights (Figure S2). The centrality indices were also stable, with their stability coefficients exceeding the recommended cut-off, 0.50 (see Figure S3).

In the depression network, the strongest edges involved symptom D1 (sadness), which was also the most central node in the network (EI = 2.47). The strongest connection in this network was between D1 (sadness) and D4 (hypersomnia) ($W = 1.33$). The latter symptom (hypersomnia) was the second most central symptom, followed by its physical sequalae; for instance, D5 (low energy/tiredness) and D7 (trouble concentrating).

In the mania network, the most central symptom was by far (three standard deviations above the mean) M7 (fleeting thoughts). Secondary manic central symptoms were behavioural in nature, for instance, M8 (inappropriate behaviour), and M10 (impulsiveness). The strongest edges in the mania network included pairs of symptoms that were functionally similar and theoretically expected: M2 (restless) with M7 (fleeting thoughts) ($W = 1.53$); M9 (increased spending of money) with M10 (impulsivity) ($W = 1.04$).

3.2 | Bipolar disorder network

Figure 2 depicts the Ising network of bipolar symptomatology, the shortest pathways linking its two communities, and the expected influence and bridge centrality metrics of all symptoms. From the 276 possible parameters, our cross-validation procedure screened out 146 (53%) of them (see Figure S3). The remaining 130 edge-weights, which were the most replicable (>95% replicability), are visualized in Figure 2.

In the bipolar model, the depressive and manic symptoms exhibited more connectivity within their respective syndromes, compared to their opposing syndrome. Our two community-detection algorithms, *walktrap* and *spinglass*, statistically validated this visual observation by revealing that the depressive and manic symptoms dispersed into their theoretically expected communities. Notably, the expected influence patterns of the bipolar network paralleled those of the intra-syndromic models by pointing to the same central symptoms, that is, D1 (sadness) and M7 (fleeting thoughts).

This model also revealed several notable links between depression and mania, of which the second figure highlights the shortest (/strongest) ones. From the highlighted shortest paths, three main themes can be drawn. First, D4 (hypersomnia) was linked to M4 (manic insomnia) ($W = 0.32$); both of these were linked to their respective physical symptoms; for instance, the D7 (concentration problems) ($W = 0.61$) and D6 (talkativeness) ($W = 0.8$), respectively.

Second, D3 (anhedonia) was robustly linked to M10 (impulsiveness) ($W = 0.13$). The former mapped onto the emotional aspects of depression; for instance, sadness ($W = 1.10$) and suicidal ideation ($W = 1.16$). Crucially, the latter (M10) was associated with similar behavioural aspects of mania, such as increased spending of money ($W = 1.12$), which further mapped onto depression's emotionality (e.g., suicidal ideation) ($W = 0.24$).

Finally, D12 (suicidal ideation) was linked to both M9 (increased spending of money) ($W = 0.14$) and M12 (believed I was someone else) ($W = 0.25$). Interestingly, M9 and M12 shared a close relationship by being spatially proximal and exhibiting similar relations to various other manic symptoms indicating hyperactivity, for instance, M11 (exaggerated confidence), M3 (excessive friendliness), M5 (increased sex interest), and the aforementioned symptom M10 (impulsivity) (average $W = 0.23$; range {0.20–0.30}).

3.3 | Diagnostic utility and centrality

Our machine learning (random forest) algorithm revealed the importance of each symptom in predicting lifetime episodes of depression and mania. These importance scores (which quantify symptom diagnostic utility) are graphically outlined in Figure 3, from which it can be seen that our identified central and bridge

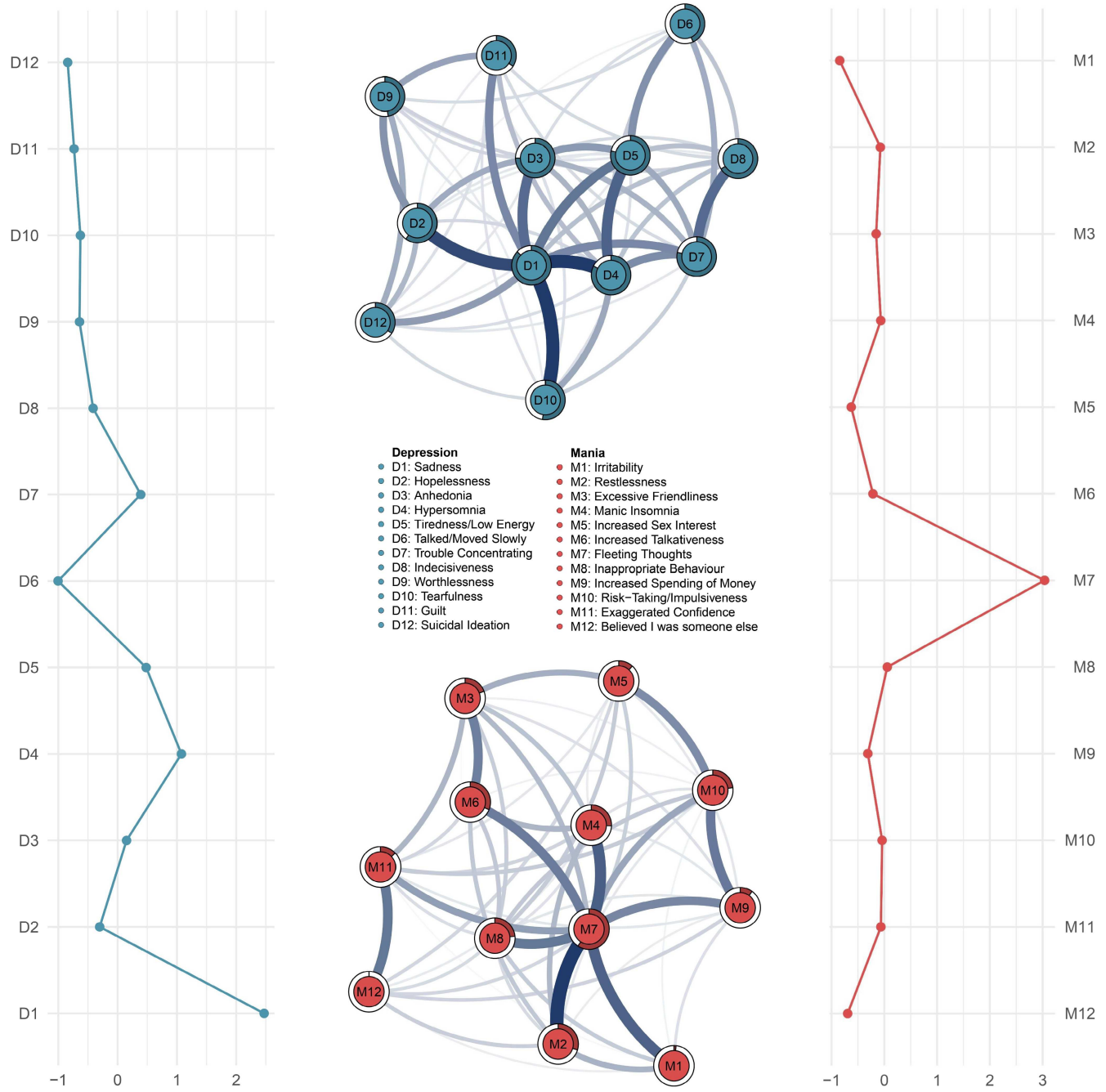

FIGURE 1 Ising network models and centrality plots of depression and mania symptomatologies. The top and bottom panels represent, respectively, the Ising network models of depression and mania. All connections among symptoms were positive (dark blue colour). The thickness of the edge denotes the strength of the relation between symptoms. The expected influence centrality indices (which denote the sum of raw edge weights) are displayed on the left (for depression) and right (for mania).

symptoms are among the strongest predictors. In particular, D1 (sadness) was the most important predictor of lifetime depressive episodes, followed by D4 (hypersomnia) and D3 (anhedonia). Similarly, M7 (fleeting thoughts) was the most important predictor of lifetime manic episodes, followed by M2 (restlessness) and M4 (manic insomnia). These observations were validated by the strong correlations between these diagnostic scores with their depressive and manic centrality indices (Spearman's rho = 0.87, 76, respectively, both $ps < 0.001$). Central and bridge symptoms in the bipolar model were also predictive of lifetime episodes of mania (in a model where all such symptoms were included); however, only the standard centrality metric was significantly related to diagnostic utility (Spearman's rho = 0.47, $p < 0.001$), not the bridge centrality one (Spearman's rho = 0.01, $p = 0.5$) (Figure 3). These patterns were robust to a sensitivity check, using binomial logistic regression (Supplement II).

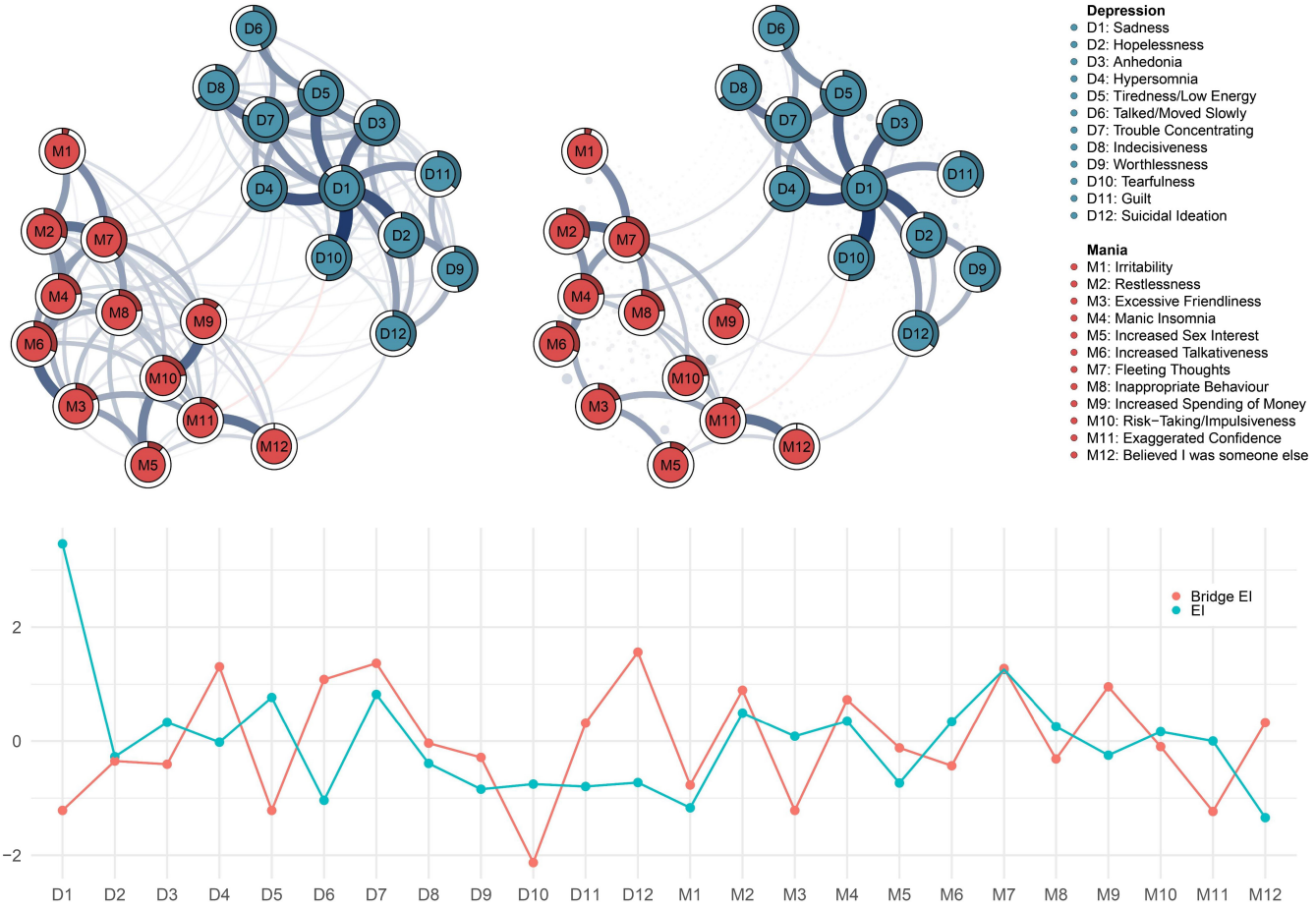

FIGURE 2 Ising network model of bipolar symptomatology (i.e., both depression and mania) (top left), shortest paths between depression and mania (top right), and bridge and expected influence centrality indices of all symptoms (bottom panel). The network at the top left represents the average relational structure of the 24 bipolar symptoms (95% replicated edges over 100 iterations). Positive links are denoted by dark blue; negative links (of which there is only one; namely, M11–D10) are denoted by red. The thickness of the edges denotes the strength of the association between symptoms.

4 | DISCUSSION

To our knowledge, this is the first study attempting to identify relations between the two bipolar poles in a large, epidemiological sample, using network and machine learning approaches. Our aim was to map the statistical constellation of depressive and manic symptomatologies, both individually and jointly. By focusing our analyses at the symptom level, we were able to reveal central symptoms of the manic and depressive syndromes, as well as symptoms which bridge their boundaries and thereby contribute to bipolarity. By leveraging machine-learning methods, we validated the diagnostic utility of our centrality metrics. Below, we outline each finding in turn, discuss its relation to past network research, and conclude with a discussion on present limitations and future directions for network analysis on bipolar disorder.

First, we have revealed several central facets within the two bipolar poles, and in bipolar disorder, broadly. In the depression network, the most central symptom was sadness, followed by hypersomnia, as well as its corresponding physical sequala (such as concentration problems and tiredness). These centrality patterns parallel those of previous research, which has pointed primarily to emotional and secondarily to physical symptoms as being the most interconnected aspects within depression networks.[48–50] By contrast, the centrality of mania involved primarily cognitive and physical aspects of mania (e.g., 'racing thoughts' and 'restlessness,' respectively) and, secondarily, behavioural ones relating to impulsivity. Two previous studies have pointed to similar central facets in mania, including not only 'raced thinking'; but, also, 'talkativeness', 'increased levels of energy', and 'sex interest'.[17,18] Interestingly, in factor-analytic studies, these manic features tend to aggregate into a factor known as 'psychomotor agitation',[1] which is strongly related to impulsivity (that was similarly central here). Crucially, the bipolar model exhibited much the same centrality (that is, 'sadness' and 'fleeting thoughts'), further mirroring previous centrality findings from clinical settings.[19–22]

It is notable that our centrality findings converge with those derived in clinical samples. Despite obvious differences in sampling, symptom measurement, and also estimation methods, our centrality patterns converged with past research, pointing to indicators of hyperactivity (or psychomotor agitation) as the being central to mania and bipolar disorder. Some differences in centrality are expected across studies, given the use of different measurement

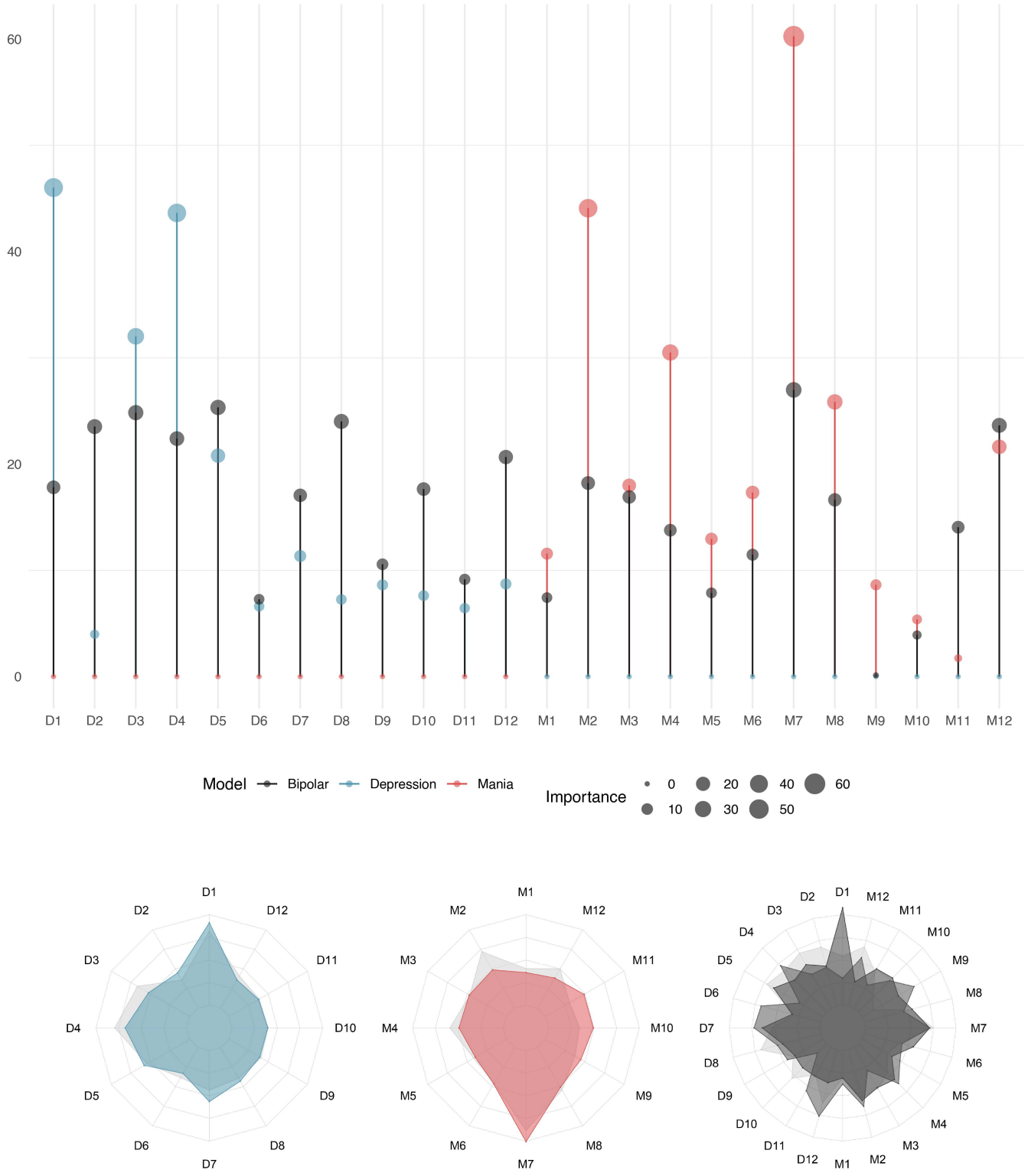

FIGURE 3 Top panel depicts the variable importance plot, from the machine-learning procedure, depicting the diagnostic utility of symptoms in predicting either depression or mania, in three models: one with lifetime episodes of depression being regressed on depressive symptoms only (blue); another with lifetime episodes of mania being regressed onto the manic symptoms only (red); a final one whereby lifetime episodes of mania (indicating bipolar disorder) were regressed onto all symptoms (black). Bottom panel graphically outlines the relation between depression's centrality (blue) and its symptoms' diagnostic utility (light grey); mania's centrality (red) and its symptoms' diagnostic utility (again, light grey), and bipolar disorder's centrality (black) and bridge centrality (dark grey), with its diagnostic utility (again, light grey). Expected influence centrality, but not bridge, indices were robustly related to diagnostic utility.

instruments. For example, even though two previous studies included psychomotor speed in their networks (both revealing that it was central in mania/bipolar disorder), one of them conceptualized such speed in terms of goal-directed activity,[51] whereas the other one did so in terms of speed of speech.[52] Other differences may also be expected, given underlying population differences. For example, 'talkativeness' and 'thinking faster' were consistently shown to be central facets of hypomanic symptoms[17]; distinguish individuals with bipolar disorder type II from those with type I[18]; and, finally, be central facets in individuals with a bipolar diagnosis who are minimally impaired.[53] By contrast, centrality in more severe samples (such as those with bipolar Type I) was shown to be reflective of more 'severe' indicators of mania; for instance, increased interest in sex[18] or suicidal ideation.[53] Our results converge with these findings by pointing to 'milder' indicators of hyperactivity (that is, having 'racing thoughts' or being 'restless') as being most central to mania/bipolar disorder in the general population. Our findings are further in line with emerging evidence that implicates abnormal cognitive mechanisms to raced thinking and impulsivity, and suggest that such indicators of psychomotor agitation/speed require more attention in regard to the pathogenesis of manic episodes (and bipolar disorder, more broadly).[54,55]

A second implication of our research concerns the bridge symptoms. To our knowledge, this is the first study to explicitly examine symptoms (and the pathways thereof) that bridge depression and mania. Overall, we revealed four such symptoms: sleep disturbances, anhedonia, suicidal ideation, and impulsivity. In the network literature, such symptoms have been termed as 'bridge,' since they are thought to unify psychopathologies by spreading activation across their symptoms, thereby leading to comorbidity patterns. In our bipolar model, sleep problems (manic insomnia and hypersomnia) were influential in this manner by 'bridging' the emotional facets of depression to the physical aspects of mania. A large corpus of data has implicated sleep abnormalities in bipolar disorder.[2,56] Further evidence has also suggested that circadian disruptions during euthymic states can act as precursors to either mania or hypomania,[57] and current cognitive-behavioural interventions for bipolar disorder emphasize on establishing healthy sleep habits as a way of managing mood instability.[58] Our results are consistent with these findings and suggest that sleep problems may represent a key endophenotypic mechanism by which individuals with bipolar disorder transition from one bipolar pole to the other.

An additional pathway in the bipolar network was the one between (severe) emotional aspects of depression (namely, anhedonia; suicidal ideation) and the behavioural (for instance, increased spending of money), as well as psychological (for example, inflated self-perceptions) manifestations of impulsivity. The links between these depressive symptoms and impulsivity provide some support for the *depressive-avoidance account* of bipolar disorder, which suggests that 'manic impulsivity' represents a 'flight' from intolerable depressive states.[6,59] However, given the undirected nature of our networks, an opposing interpretation is equally plausible, with these depressive symptoms representing the dire consequences, instead of the precursors, of impulsive actions.[60] In either case, these associative patterns predict that an intervention on either set of symptoms could reduce mood transitions in bipolar disorder.

These network patterns fit neatly with recent discussions on the nosology of the bipolar spectrum and mental disorders, more broadly. For instance, similar to our network models, the ACE model provides a theoretical framework of mood at the symptom-level by conceptualizing mood symptoms in terms of three functional domains: activity, cognition, and emotion.[61] Our findings point to the former two domains as being most central to mania (and bipolar disorder), and the latter as most central to depression. Similarly, our bridge symptoms involved relations between emotion (anhedonia; suicidal ideation) and activity (impulsivity), on the one hand, and activity (sleep problems) and cognition (raced thinking), on the other. This provides a clear picture of how these functional domains relate to each another—one that could be further painted through longitudinal network models (that can help reveal the chronology of these relations).[62] To this end, related research domain criteria (RDoC) could also be used.[63] Although the RDoC and network approaches operate at different levels of analysis (the former biological; the latter psychological), both converge in their transdiagnostic conception of psychopathology.[64] Arguably then, the two could be fruitfully combined to investigate both the phenomenology of bipolarity (via network models)[52] and its neurobiological underpinnings (via related RDoC).[65]

The final implication of our work includes our use of machine-learning to showcase the diagnostic utility of central symptoms. In particular, our random forest algorithm revealed that central and bridge symptoms (from all models) were the most important predictors of lifetime episodes of depression and mania. This result replicates past research that has also highlighted the utility of centrality indices in predicting post-treatment outcomes,[13] as well as future mental disorder diagnoses.[14] Notably, compared to bridge centrality indices, the expected influence ones mapped better onto our measure of diagnostic utility, suggesting that central symptoms are a better proxy of diagnostic importance. Albeit unexamined, it could be intuited that bridge symptoms map better onto outcomes of (general) impairment, as they are thought to quantify burdens of comorbidity.[44] Future research could utilize our current machine learning pipeline to clarify the conceptual distinction between central and bridge symptoms.

Despite the strengths of our study, several limitations must be acknowledged. Our study was the first, to our knowledge, to reveal symptoms that bridge the two bipolar poles. However, caution must be taken when interpreting these statistical patterns. Although we have noted that some symptom paths represent transitional mechanisms between depression and mania (manic impulsivity to depression's emotionality, for instance), we must acknowledge that mediational inferences of this sort should be considered tentative until supported by further data, preferably of experimental nature. To avoid 'Berkson's bias,' differences between this and clinical studies have been interpreted in terms of population differences.[66] Ideally, however, formal procedures should be used to ascertain the

nature of differences between clinical and community samples (for instance, whether they are a function of different probability distributions).[25] Finally, we note that our results were drawn in a Canadian representative cohort, and may thus necessitate replication in other general populations.

Our limitations notwithstanding, the degree of convergence between our results and those derived in clinical samples provides considerable confidence in ways forward. Crucially, this degree of confidence may be more appropriately ascribed to 'global' (e.g., centrality metrics) rather than 'local' (e.g., particular edge paths) network features, which have been demonstrated to be more robust to Berkson's bias (and population differences).[67] Further research in clinical samples is required to ascertain whether our highlighted endophenotypes (namely, impulsivity, sleep disturbance, and severe emotionality) are influential in 'bridging' the two poles of bipolar disorder. To this end, recent advances in network psychometrics can be used in 'confirmatory' research. For example, recent methods which allow for 'meta-analysing' network structures or incorporating 'prior' network information for confirmatory network testing could be employed to scrutinize the current statistical trends in clinical samples.[68] Additionally, such research can be benefited by experimental approaches. Targeted interventions for common issues in bipolar disorders (such as sleep, interpersonal, and mood ones) are already in place.[58] Applying formal mediation,[69] machine-learning,[70] and longitudinal network[62] methods during such interventions could elucidate symptom-level mechanisms that are implicated in treatment outcomes. Thus far, a limitation of network psychometrics has been its exploratory use. As we are transitioning into the second decade of psychological network research, replication of existing symptom network structures will be of vital importance—not only for validating their proposed dynamics, but, more so, for translating them into formal theories on how various psychopathologies operate.[68]

To conclude, our study has highlighted, for the first time, symptoms that bridge the two bipolar poles in a large sample, representative of the Canadian population. In particular, paths that linked sleep disturbances (insomnia and hypersomnia), as well as emotional symptoms of depression (anhedonia and suicidal ideation) with manic impulsivity, were detected. Centrality patterns here replicated previous findings from clinical populations, by pointing to indicators of emotionality (e.g., sadness) and hyperactivity (e.g., raced thinking) as being most central to depression and mania, respectively. Finally, our machine-learning algorithm demonstrated that central symptoms hold the highest diagnostic utility with regard to predicting lifetime episodes of depression/mania. Bridge symptoms were also influential in this regard; however, they were also hypothesised to map better onto measures of general impairment. These statistical patterns highlight influential (endo)phenotypes to bipolarity, which, if replicated, could point to fruitful targets for prevention and intervention strategies on bipolar disorders.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Access to the data supporting this study (namely, the Canadian Community Health Survey, the Mental Health and Well-Being component; 82-617-XIE) is available through Statistics Canada Research Data Centres (please see https://www.statcan.gc.ca/en/start). The authors confirm that summary statistics for replication of current statistical trends (for instance, weighted adjacency matrices) are available on OSF: https://osf.io/s3kzg/. Raw data were not made publicly available due to our data-sharing agreements with Statistics Canada.

ETHICS STATEMENT

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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