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Predictors, symptom dynamics and neural mechanisms of bipolar disorders

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CHAPTER 5

Dynamic time warp analysis of individual symptom trajectories inpatients with bipolar disorder

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Abstract

Background
Manic and depressive mood states in bipolar disorder (BD) may emerge from the non-linear relations between constantly changing mood symptoms exhibited as a complex dynamic system. Dynamic Time Warp (DTW) is an algorithm that may capture symptom interactions from panel data with sparse observations over time.

Methods
The Young Mania Rating Scale and Quick Inventory of Depressive Symptomatology were repeatedly assessed in 141 patients with BD, with on average 5.5 assessments per patient every 3 to 6 months. DTW calculated the distance between each of the 27∗27 pairs of standardized symptom scores. The changing profile of standardized symptom scores of BD patients was analyzed in individual patients, yielding symptom dimensions in aggregated group-level analyses. Using an asymmetric time-window, symptom changes that preceded other symptom changes (i.e., Granger causality) yielded a directed network.

Results
The mean age of the patients was 40.1 (SD 13.5) years old, and 60% were female. Idiographic symptom networks were highly variable between patients. Yet, nomothetic analyses showed five symptom dimensions: core (hypo)mania (6 items), dysphoric mania (5 items), lethargy (7 items), somatic/suicidality (6 items), and sleep (3 items). Symptoms of the 'Lethargy' dimension showed the highest out-strength, and its changes preceded those of 'somatic/suicidality', while changes in 'core (hypo)mania' preceded those of 'dysphoric mania'.

Conclusion
DTW may help to capture meaningful BD symptom interactions from panel data with sparse observations. It may increase insight into the temporal dynamics of symptoms, as those with high out-strength (rather than high in-strength) could be promising targets for intervention.

5.1 Introduction

Bipolar disorder (BD) is a chronic psychiatric illness with alternating episodes of depression and (hypo)mania[1]. The symptom presentation of BD is heterogeneous, and apparent sub-phenotypes often show a different prognosis, course of illness, and treatment response[2]. Several studies showed that symptomatology, severity, polarity, and cycling patterns of episodes differed strongly between patients with BD[3, 4], whereas recurrent episodes within a patient often seemed to present a similar pattern of symptomatology[5]. In addition, patients with BD (either type I or II) can suffer from rapid cycling, psychosis, and mixed mood episodes[6]. Taking all these together, it is obvious that it is challenging for clinicians to diagnose BD and target interventions for each individual. One of the important aims in the treatment of BD is to identify the individual patterns of so-called prodromal "warning" symptoms and address these symptoms as early as possible to prevent recurrent episodes. Although the clinician and patient try to grasp the individual symptom dynamics in early warning plans, these are often based on retrospective knowledge and subjective interpretations of how a new mood episode could have developed in the recent past. Repeated symptom registrations and analyses of these individual data, might lead to more insight into the individual symptom dynamics and allows for more accurate interventions to prevent new mood episodes.

It is challenging to gain insight into the temporal directional relationships between mood symptoms (either depression or mania), both in individual and in groups of patients with BD. In the majority of studies in BD, sum scores of manic and depressive symptoms with a threshold are used to indicate case status, and life charts are used to register the flux of mood states over time[7]. Moreover, such epidemiological approaches are mostly group-based, and the patterns found may not be applicable to the individual patient[8, 9]. Besides, it is often assumed that BD results from an underlying common cause, but this approach does not take into account that symptoms themselves might also interact and be causally depending on one another in the direction of the relation of certain symptoms[10, 11]. The course of BD is often unpredictable, not because it is random, but because its current behavior depends on a unique path of interactions with the internal and external context. A simple example of this in BD is that lack of sleep in BD often leads to increased energy and/or activity, which in its turn leads to more lack of sleep. BD can be approached as a complex dynamic system[12, 13] in which there are complex dependencies in time between constantly changing components (such as mood symptoms and environmental factors), across multiple levels of organization and scale. These components together form the behavior of the whole, such as manic, euthymic, and depressive mood states, as emergent phenomena.

Dynamic time warp (DTW) is a computational algorithm that could be used to process individual symptom data and takes account of potential non-linear dynamics among symptoms and focuses on change profiles rather than absolute levels of symptom scores[14, 15]. This method is a widely used statistical algorithm[16], but not in the field of psychiatry and psychology[15]. This method helps us to investigate the symptom interconnection within panel data, also when there are only a parse number of time points. It starts with analyzing individual patient data (i.e., idiographic approach, individual level) after which these are aggregated (i.e., nomothetic analysis, group level). This is important as BD is a multicausal, dynamic, and idiosyncratic disorder, for which personalized approaches are

needed to target those symptoms that directly affect other symptoms[11, 17, 18]. The symptom network approach can help to analyze and visualize the interconnection of symptoms, which may explain the switching of mood states[19]. Sudden switches between relatively stable mood states are referred to as critical transitions, catastrophic phenomena, or tipping points in the field of complex systems[11, 13, 20]. In addition, using this network approach, it will be possible to provide patients with their own unique symptoms profile which enables them and their caregivers to gain more insight into their symptom dynamics.

So far, DTW has only been used to study unipolar depression[14, 15, 20, 21], but no study has focused solely on BD. To our best knowledge, only two cross-sectional network studies examined the mood symptoms in BD.[22, 23] The first study[22] studied 195 BD patients and participants at high risk and found that symptoms were most strongly interrelated with symptoms at the same mood pole, and the most central symptoms among the BD network were symptoms measuring the level of energy or activity. In the second study,[23] 125 patients with BD were allocated into three longitudinal clinical courses (minimally impaired, depressed, and cycling). Their results showed that in severe courses of illness the mood symptoms were most strongly interconnected. These two studies had cross-sectional designs, meaning that the temporal dynamics of symptoms were not investigated.

In the current study, we use DTW to analyze the dynamics of symptoms over time in the patient sample previously used for the cross-sectional network analysis[23]. In this study, we utilized symptoms of BD repeatedly (every 3 to 6 months) to assess depression and manic symptoms in 141 patients with BD. We aimed to present the first implementations of DTW time-series analysis on BD symptoms trajectories. Both individual level (i.e., idiographic) and group level (i.e., nomothetic) analyses are presented.

5.2 Method

5.2.1 Study sample

Data were derived from a 2-year longitudinal study among 181 adult bipolar outpatients, with a diagnosis of BD I or BD II (based on DSM-IV), who were treated by the Outpatients Clinic for Mood Disorders in the Hague (the Netherlands). The exclusion criteria were schizo-affective disorder, neurological diseases, and substance abuse disorder. All participants signed the written informed consent before enrollment and the study was approved by the Medical Ethical Committee Mental Health Care Organizations Rotterdam (number 7220) and the Central Committee Human Studies (number NL18286.097.07). The study design of this cohort has been described previously[23].

5.2.2 Measurements

For the current study only data of mood assessments of depressive and manic symptoms were used. These two measurements were assessed at baseline and subsequently every 3 to 6 months yielding up to 6 measurement points (at baseline, 6, 12, 18, 21, and 24 months) per participant.

Depressed symptoms
Depressive symptoms were assessed by the 16 items Quick Inventory of Depressive Symptomatology (QIDS-SR)[24]. Each item is rated 0-3. The QIDS-SR total score ranges from 0 to 27, with scores of 5 or lower indicative of no depression, scores from 6 to 10 indicating mild depression, 11 to 15 indicating moderate depression, 16 to 20 indicating severe depression, and total scores greater than 21 indicating very severe depression. This self-report questionnaire has good internal consistency (Cronbach's alpha > 0.86). Cronbach's alpha in the current study was 0.80 at baseline.

Manic symptoms
For the assessment of manic symptoms, the clinician-rated, 11-item Young Mania Rating Scale (YMRS)[25] was used. The items are rated based on the patient report and the clinical impression of the interviewer. There are four items rated 0-8 (irritability, speech, thought content, and disruptive/aggressive behavior), while the remaining seven items are rated 0-4. The YMRS total score ranges from 0 to 60 with scores from 13 to 19 indicating minimal symptoms, 20 to 25 indicating mild mania, 26 to 30 indicating moderate mania and 38 to 60 indicating severe mania. The YMRS has good inter-rater reliability (r=.93).[25] Internal consistency (Cronbach's alpha) in the current sample was 0.79 at baseline.

5.2.3 Statistical analysis

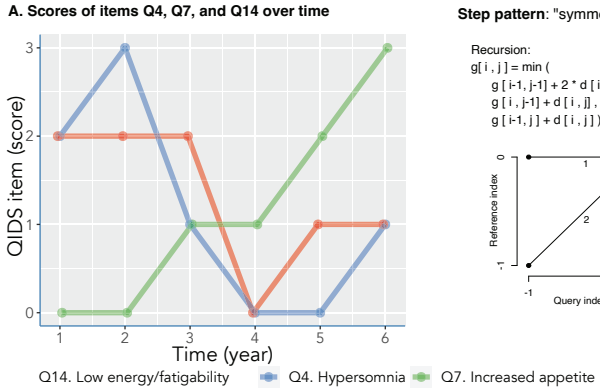
Sociodemographic and clinical variables at baseline are summarized as means and standard deviations (SD) or percentages, as appropriate.

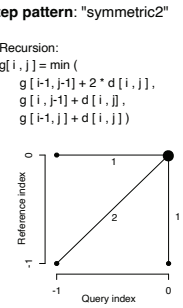
Time-series panel data were gathered, which consisted of 27 depressive and manic symptom ratings assessed on the same time scale. Participants who had 3 or less of the mood assessments were excluded, which resulted in 141 participants who were included in the

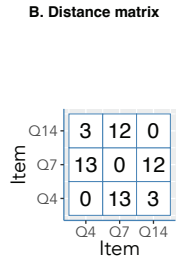
current analyses. When we compared these 141 participants with 38 having 3 or fewer assessments, no significant differences were found in terms of age or gender (p-value for age 0.73; for gender 0.56).

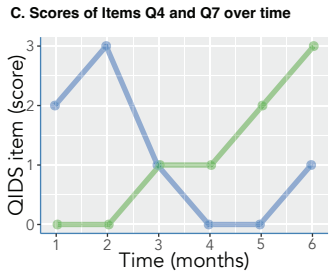
DTW was used to assess the similarity of symptom dynamics within participants, both in undirected and directed (in time) analyses. When the trajectories of the severity of a symptom pair showed large similarities, the resulting distance will be small, whereas when these changes over time are rather erratic and independent, their distance will be large. DTW is thus a shape-based time-series clustering technique. All item scores were group-level standardized before the analyses, in order to let the results be based on the relative changes over time.

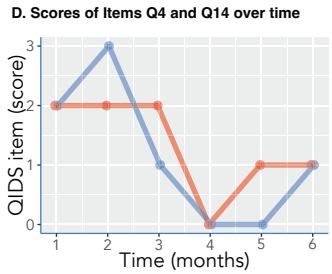
Within each patient (i.e., idiographic approach), we used DTW to calculate each "distance" between each pair of symptoms, based on the optimum warping path between two series under certain constraints, as described in detail in Figure 5.1. For the undirected analyses, this resulted in a 27 by 27 symmetric distance matrix for each individual. A low distance represents a time series of item scores that are very similar, whereas a high distance represents dissimilar item dynamics over time. The time window was set at 1, meaning that similar changes between t-1, t, and t+1 were taken into account. A dissimilar score at the start and end of each time series could have a disproportional effect on the total distance because these cannot be dynamically aligned. Therefore, interpolation of 5 values between each time point was applied before calculating the distance, which subsequently reduced the disruptive effect of starting and endpoints mismatches. Moreover, there is a tendency of scores that remained zero throughout follow-up to cluster strongly together, therefore for each pair of symptoms that scores zero on each time point we added a penalty of distance 1 to the final distance of that symptom pair in that participant. This patient level analysis resulted in 141 individual distance matrices.

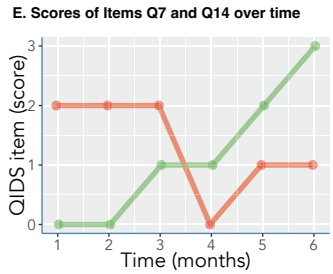

A. Scores of items Q4, Q7, and Q14 over time
QIDS item (score)
Time (year)
Q14. Low energy/fatigability
Q4. Hypersomnia
Q7. Increased appetite

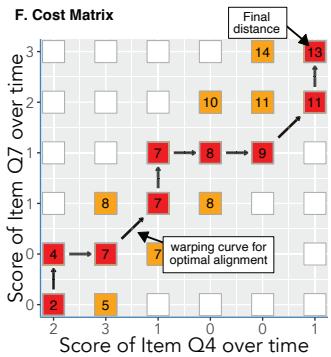

Step pattern: "symmetric2"
Recursion:
g[i , j] = min (
g [i-1, j-1] + 2 * d [i , j] ,
g [i , j-1] + d [i , j] ,
g [i-1, j] + d [i , j])
Reference index
Query index

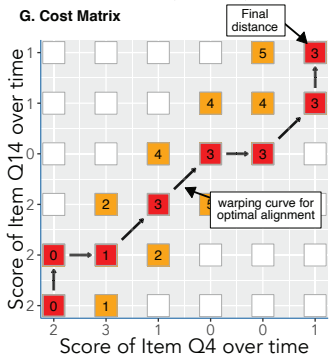

B. Distance matrix
Item
Q14
Q7
Q4


C. Scores of Items Q4 and Q7 over time
QIDS item (score)
Time (months)


D. Scores of Items Q4 and Q14 over time
QIDS item (score)
Time (months)


E. Scores of Items Q7 and Q14 over time
QIDS item (score)
Time (months)


F. Cost Matrix
Final distance
warping curve for optimal alignment
Score of Item Q7 over time
Score of Item Q4 over time


G. Cost Matrix
Final distance
warping curve for optimal alignment
Score of Item Q14 over time
Score of Item Q4 over time

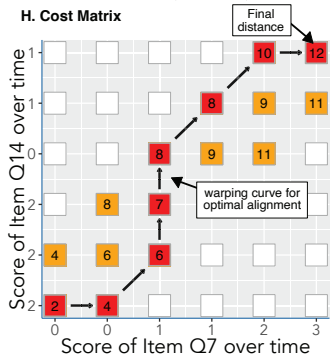

H. Cost Matrix
Final distance
warping curve for optimal alignment
Score of Item Q14 over time
Score of Item Q7 over time

Figure 5.1: Explanation of the dynamic time warp analysis (DTW), an algorithm for measuring similarity between two time series. We analyzed three QIDS symptom scores over time. In panel [A] the (unstandardized) scores of these individual items are given over time during the follow-up. We used the shape-based time-series clustering technique of DTW, to yield the distance as a dissimilarity measure. It aims to find the optimum warping path between two time series. The first step in DTW involves creating a local cost matrix (LCM), which has 6×6 dimensions (as we had 6 assessments in time). In the seconds step, the DTW algorithm finds the path that minimizes the alignment between the two item scores by iteratively stepping through the LCM, starting at the lower left corner (i.e., LCM[1, 1]) and finishing at the upper right corner (i.e., LCM[6, 6]), while aggregating the total distance (i.e., 'cost'). At each step, the algorithm takes the step in the direction in which the cost increases the least under the chosen constraint. The constraint was the Sakoe-Chiba window of size one, with one time-point before and after the current assessment. The way in which the algorithm traverses through the LCM is dictated by the chosen step pattern, in our case the default "symmetric2" step pattern [B]. Parts [C], [D], and [E] explain the calculations of dynamic time warp distances for the three symptom pairs, yielding 10, 8, and 1 as for their respective distances. We can conclude that the green and red lines show a more similar route over time (with a distance of only 3), which is represented by the smaller distance compared to each distance with the red line (with distances of 10 and 8).

The 141 individual distance matrices were subsequently analyzed on the group level (i.e., nomothetic approach), through a Distatis three-way principal component analysis[26]. The Distatis analysis yielded principal components that are called compromise factors, of which the first three explain the largest amount of variance (used as x, y, and z in the 3-dimensional supplementary plot). These compromise factors thus best describe the similarity structure of the 141 distance matrices. The compromise factors were used as coordinates of the 27 symptoms as points such that the distances in the map best reflect symptoms covarying with its nearest neighboring symptoms[27]. The first against the second, and the first against the third compromise factors were plotted into the x-y planes, and the three compromise factors were also plotted in a supplemental three-dimensional interactive plot.

A hierarchical cluster analysis was applied according to 'Ward.D2' clustering methods, which was visualized in a dendrogram. Ideally, all items of the same dimension are similar to each other but are as dissimilar as possible from items in a different dimension. To estimate the optimal number of dimensions, elbow and silhouette plots were used. The elbow can be observed as a sharp change in the slopes of adjacent line segments, which location might indicate a good number of dimensions to retain. The silhouette method calculates the average distance of each item to the items in the same dimensions as well as the average distance to the items in the nearest cluster, with a plot of the average scores over all items against a different number of dimensions. The number of dimensions yielding the highest average silhouette score is the best number of dimensions[28].

For the directed analyses of symptom dimensions scores, the same DTW algorithm was used as for the undirected analyses, except for a crucial difference. The window type using the Sakoe-Chiba band[16] was specified as being asymmetric, such that the flow of information was assessed in one direction, from dimension 1 to dimension 2, but not vice versa. For each of the 141 patients, a directed distance matrix was calculated for the standardized sum scores of the 5 dimensions. A directed network plot was plotted from the resulting distance matrix that was the average of the 141 directed distance matrices. Two standardized metrics of node centrality were derived: in-strength centrality and out-strength centrality. The directed edges are represented by arrows, with tips pointing in the temporal direction (which is a prerequisite for a causal relationship). Out-strength centrality refers to the number and strengths of outgoing edges that depart from a specific node (i.e., in our DTW analysis an item with a high out-strength score implies that item changes tend to precede changes in other item scores). In-strength centrality refers to the number and strengths of incoming edges of a specific node (i.e., in our DTW analysis an item with a high in-strength score implies that its changes tended to follow upon changes in other item scores).

To assess whether our undirected analyses yielded reliable results, we did a random split on the data and repeated the analyses in both subsets. This helped us to determine whether this resulted in similar findings or discrepant results, which may signal unreliable findings. Node placement was done by using the Procrustes algorithm (from the R package 'networktools'), to aid the visual comparison between the two networks. This was only available for undirected analyses using symmetric distance matrices. The congruence coefficients (with the 2.5th and 97.5th percentiles) were estimated, through bootstrapping of 200 random splits of the 141 participants. A value below 0.85 indicates poor similarity,

a value in the range of 0.85 to 0.94 indicates fair similarity, and a value of 0.95 can be considered as being equal[29].

Descriptive analyses were done with SPSS version 25 (IBM Corp Released 2017, IBM SPSS Statistics for Windows, Version 25). Network analysis were done with the packages "dtw" (version 1.22-3), "parallelDist" (version 0.2.4), "qgraph" (version 1.6.9), “stats" (version 4.0.3), "networktools" (version 1.2.3), and the 'plotly' package (version 4.9.4.1) for the R statistical software (R version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.r-project.org/). A sample R script for the DTW analyses is provided as supplementary material and can be downloaded here: https://osf.io/6nmtk.

5.3 Results

The baseline characteristics of the 141 patients are shown in Table 5.1. The mean age was 49.1 years with a standard deviation (SD) of 13.5. The majority of the patients were female (60%). The mean score of baseline QIDS and YMRS were 7.9 (SD 5.1) and 1.8 (SD 3.2), respectively, indicating mild depressive symptoms and no manic symptoms. This is due to the fact that most patients were euthymic at study entry.

5.3.1 Individual patient analyses (idiographic approach)

We used DTW clustering method to analyze data from each participant. Here, only three exemplar patients were selected from the full data-set, to demonstrate how DTW can be applied on the individual patient level (Figure 5.2 for patients A, B, and C). These three patients show a high degree of inter-individual variability in their symptom trajectories. In patient A there was a tight clustering of mania symptoms, whereas in patient B there was a tighter clustering of depressive symptoms. Patient C showed two separate symptom dimensions, one of the depressive symptoms later transitioning into one of the manic symptoms.

Patient A was a 51-year-old female (bipolar disorder type I) with onset of depression at 37 years and onset of mania at 41 years of age. Her dendrogram shows a prominent clustering of mania symptoms. In assessments 2 and 3 'pressured speech' was her most prominent symptom. The network graph shows that changes in symptoms of 'dysphoric mania' (blue symptoms) and 'core (hypo)mania' (red symptoms) and a few of 'somatic/suicidality' (purple symptoms) were mostly in phase over time. Most symptoms of 'lethargy' (green symptoms) were only loosely connected to her symptom network.

Patient B was a 60-year-old female (bipolar disorder type II) with onset of depression at 20 years and onset of hypomania at 26 years of age. Her dendrogram shows a more prominent clustering of depressive symptoms, starting with high ratings on 'sad mood', later followed by higher ratings of 'Psychomotor agitation' and 'Mid-nocturnal insomnia'(see Figure 5.2B.B). She had very low ratings for YMRS items measuring the (hypo)manic symptoms, several items of YMRS could not be included in her Dendrogram, because ratings remained zero throughout follow-up. Her individual network graph demonstrated the similarity of changes over time only for the symptoms of 'somatic/suicidality' (purple symptoms) and 'lethargy' (green symptoms).

Patient C was a 59-year-old female (bipolar disorder type I) with late-onset mania at 39 years of age and late-onset depression at 49 years . Her dendrogram shows a relatively stronger clustering of symptoms than patients A and B. Symptoms with the highest severity scores at the first 3 assessments were 'mid-nocturnal insomnia' (orange symptoms) and 'poor concentration/indecisiveness' (green symptoms). Later, the strongest connections were between symptoms of 'core (hypo)mania'.

5.3.2 Group-level analysis (nomothetic approach)

The nomothetic analysis of the 141 patients is shown in Figure 5.3. The elbow and silhouette plots indicated that five dimensions fitted the data best, mainly based on the average silhouette score (Figure 5.3A). The results of dendrogram hierarchical cluster demonstrated five dimensions of symptoms (see Figure 5.3B). These were based on all 27 individual items were: (1) core (hypo)mania (6 items: 'pressured speech', 'irritability', 'elevated mood', 'increased activity/energy', 'low need for sleep and fast thought content'), (2) dysphoric mania: (5 items: 'content/delusions/hallucinations', 'poor insight', 'aggressive behavior', 'poor appearance', 'high sexual interest', (3) lethargy (8 items: 'low self-esteem/guilt', 'low interest', 'psychomotor slowing', 'psychomotor agitation', 'hypersomnia', 'sad mood', 'poor concentration/indecisiveness', 'low energy/fatigability'), (4) somatic/suicidality (6 items: 'decreased appetite', 'Increased appetite', 'suicidal ideation', 'increased weight', 'early morning insomnia', 'decreased weight') and (5) sleep: (2 items: 'sleep onset insomnia', 'mid-nocturnal insomnia').

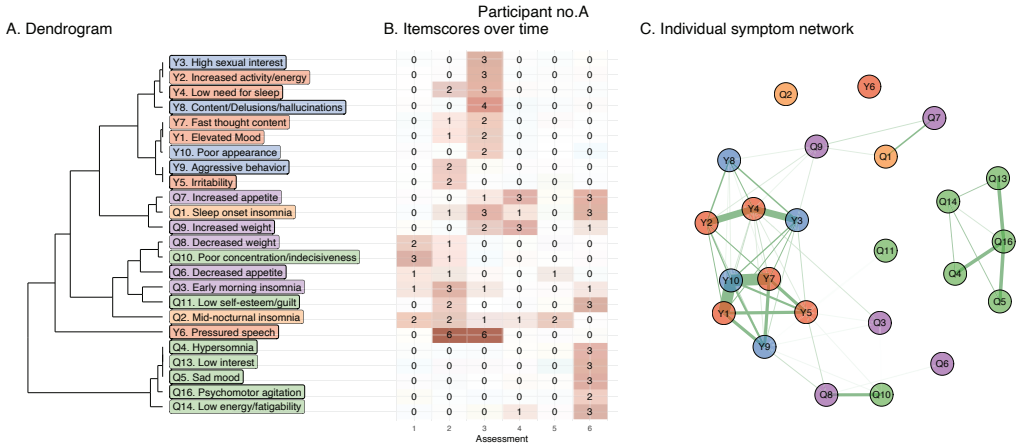
The results of three-way principal component Distasis analysis on the 141 distance matrices revealed in three principal components or 'compromise factors'. These explained 28.5%, 14.1%, and 10.2% of the variance. In a three-dimension interactive plot, a more similar change over time among patients is represented by a smaller distance between symptoms (i.e., their relative distance in the compromise space, Supplementary Figure 5.1: download here: https://osf.io/z4upr). The two compromise plots (of the first against the second compromise factor in Figure 5.3C, and of the first against the third compromise factor in Figure 5.3D demonstrate the spread of the 27 items, and show the particular strong clustering of the symptoms that were included in dimensions 1 and 2 (i.e., 'core hypomania' and 'dysphoric mania').

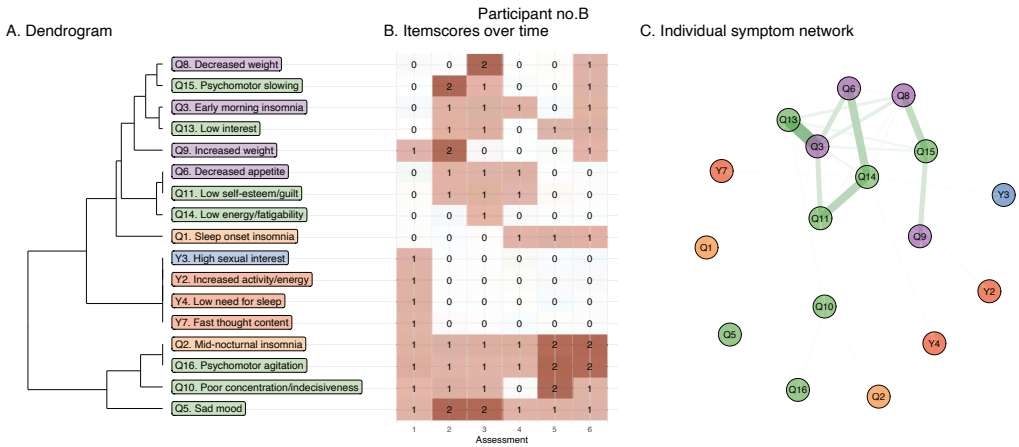
Next, a directed network was created for the changes in scores of the 5 symptom dimensions (Figure 5.4). The directed network plot showed that changes in 'core (hypo)mania' tended to precede similar changes in 'dysphoric mania', and that changes in 'lethargy' tended to precede similar changes in 'somatic/suicidality'. Dimensions 3 and 1 (i.e., 'lethargy' and 'core (hypo)mania') had the strongest out-strength centrality scores relative to the other three dimensions. Dimensions 4 and 2 (i.e., 'somatic/suicidality' and 'dysphoric mania') had the strongest in-strength centrality scores relative to the other three dimensions.

Finally, in order to validate our results of 5 symptom dimensions, we randomly split our sample of 141 patients into two samples of 70 and 71 patients. The analysis of both samples confirmed the stability of the five symptoms dimension (Figure 5.5). The median congruence coefficient was very high at 0.984 (2.5^{th} and 97.5^{th} percentiles of values) when we bootstrapped the random split procedure 200 times), supporting the high reliability of the 5 nomothetic symptom dimensions across patients.

Table 5.1: Baseline sociodemographic characteristics in 141 participants with bipolar disorder.

	(N=141)
Sociodemographic characteristics:	
Male, sex; n (%)	53 (37.6%)
Age; mean (SD)	49.1 (11.7)
Level of education: n (%)	
- Primary	29 (20.6%)
- Secondary	46 (32.6%)
- Higher	66 (46.8%)
Current smoker; n (%)	60 (42.6%)
Drugs use; n (%)	10 (7.1%)
Alcohol use; n (%)	
- none	45 (31.9%)
- 1-2 units/day	79 (56.0%)
- $\geq$ 3 units/day	15 (10.6%)
Clinical characteristics:	
Bipolar disorder type 1; n (%)	102 (72.3%)
Age of onset; mean (SD)	
Age of onset first (hypo-) mania	29.7 (10.4)
Age of onset first depression	27.0 (10.1)
QIDS baseline; mean (SD)	7.9 (5.1)
YMRS baseline; mean (SD)	1.8 (3.2)
Medication use baseline: n (%)	
- Lithium	100 (70.9%)
- Anti-epileptics	29 (20.6%)
- Anti-psychotics	36 (25.5%)
- Benzodiazepines	42 (29.8%)
- Antidepressants	51 (36.2.0%)


Participant no.A
A. Dendrogram
B. Itemscores over time
C. Individual symptom network
Y3. High sexual interest
Y2. Increased activity/energy
Y4. Low need for sleep
Y8. Content/Delusions/hallucinations
Y7. Fast thought content
Y1. Elevated Mood
Y10. Poor appearance
Y9. Aggressive behavior
Y5. Irritability
Q7. Increased appetite
Q1. Sleep onset insomnia
Q9. Increased weight
Q8. Decreased weight
Q10. Poor concentration/indecisiveness
Q6. Decreased appetite
Q3. Early morning insomnia
Q11. Low self-esteem/guilt
Q2. Mid-nocturnal insomnia
Y6. Pressured speech
Q4. Hypersomnia
Q13. Low interest
Q5. Sad mood
Q16. Psychomotor agitation
Q14. Low energy/fatigability
1 2 3 4 5 6
Assessment


Participant no.B
A. Dendrogram
B. Itemscores over time
C. Individual symptom network
Q8. Decreased weight
Q15. Psychomotor slowing
Q3. Early morning insomnia
Q13. Low interest
Q9. Increased weight
Q6. Decreased appetite
Q11. Low self-esteem/guilt
Q14. Low energy/fatigability
Q1. Sleep onset insomnia
Y3. High sexual interest
Y2. Increased activity/energy
Y4. Low need for sleep
Y7. Fast thought content
Q2. Mid-nocturnal insomnia
Q16. Psychomotor agitation
Q10. Poor concentration/indecisiveness
Q5. Sad mood
1 2 3 4 5 6
Assessment

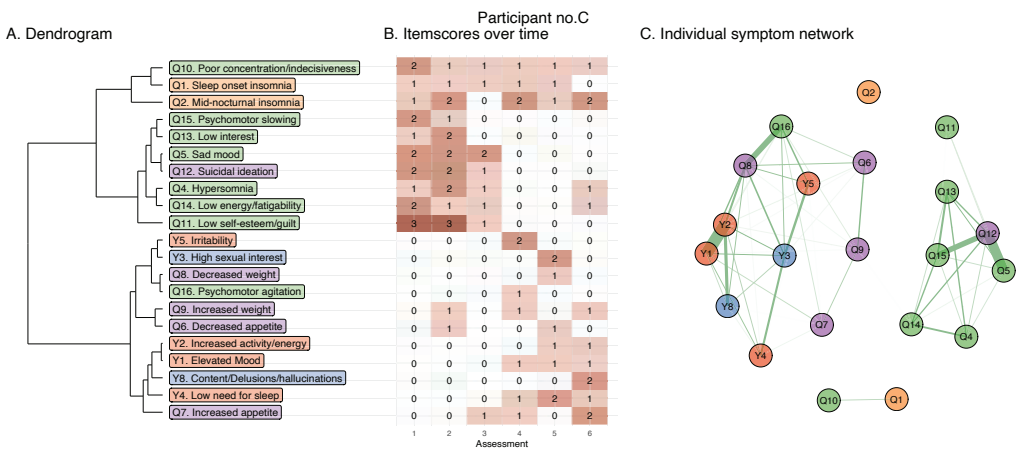

Participant no.C
A. Dendrogram
B. Itemscores over time
C. Individual symptom network
Q10. Poor concentration/indecisiveness
Q1. Sleep onset insomnia
Q2. Mid-nocturnal insomnia
Q15. Psychomotor slowing
Q13. Low interest
Q5. Sad mood
Q12. Suicidal ideation
Q4. Hypersomnia
Q14. Low energy/fatigability
Q11. Low self-esteem/guilt
Y5. Irritability
Y3. High sexual interest
Q8. Decreased weight
Q16. Psychomotor agitation
Q9. Increased weight
Q6. Decreased appetite
Y2. Increased activity/energy
Y1. Elevated Mood
Y8. Content/Delusions/hallucinations
Y4. Low need for sleep
Q7. Increased appetite
1 2 3 4 5 6
Assessment

Figure 5.2: Idiographic DTW analysis in three participants (patient A, B and C). Panels A shows the dendrogram of the clustering of symptoms with more similar trajectories over time (with the symptoms colored according to the nomothetic symptom dimensions), panels B shows the raw item scores over time every 3 to 6 months (with the severity being color coded), and panel C shows the individual symptom networks based on their DTW analysis. These samples analyses were done using unstandardized item scores to simplify the interpretation of these illustrations, whereas all other analyses were done using group-level standardized symptoms scores.

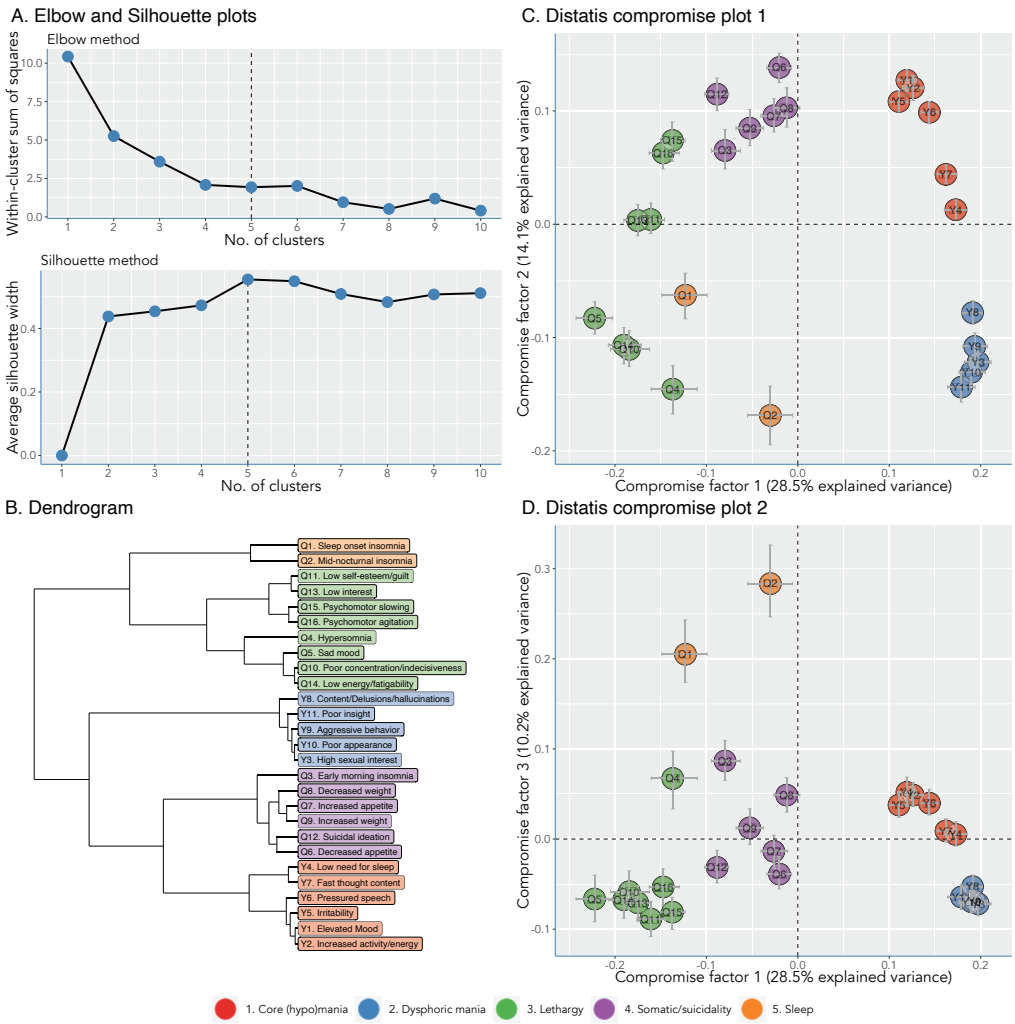


Figure 5.3: Nomothetic analyses based on all distance matrices from 141 participants. [A] A scree plot based on the elbow and silhouette method indicated five symptom dimensions. [B] A dendrogram was created, based on the Ward's (D2, i.e., general agglomerative hierarchical clustering procedure) clustering criterion on the compromise factors of the Distatis analysis of 141 distance matrices. [C] The Distatis analysis yielded three compromise factors. The position of each of the 27 BD items are shown in x-y scatter plot of the compromise space according to the first and second compromise factors, and [D] the first and third compromise factors. Error bars represent the 2.5 th and 97.5 th percentile values, derived from 500 bootstrapping resamplings.

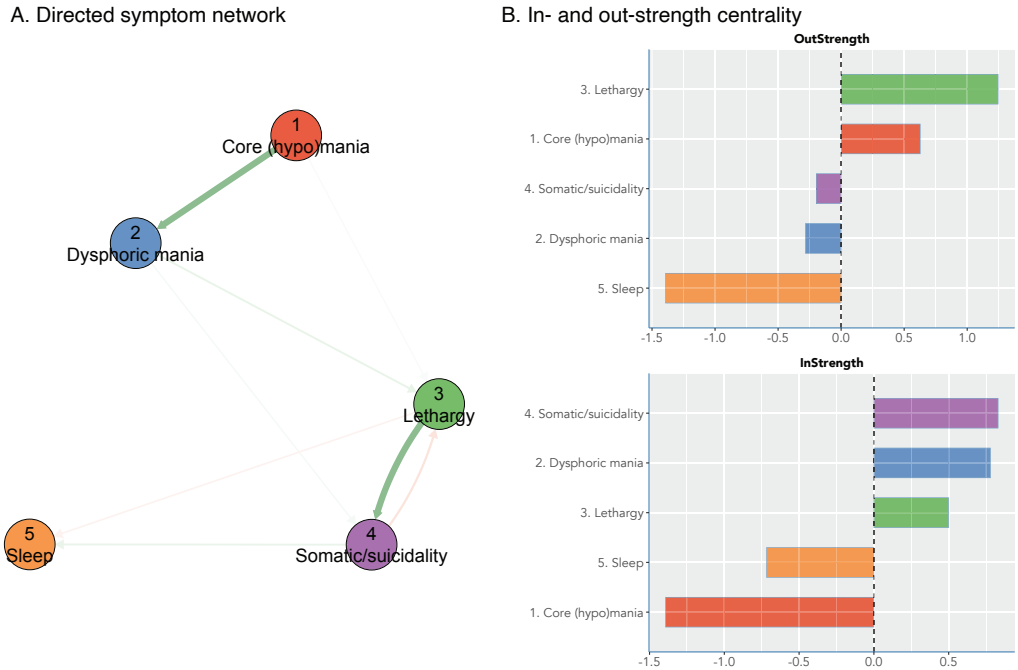


Figure 5.4: Directed symptom network in 141 BD patients. In a directional network, the flow of information is in one direction, from one node to another. The edge thickness represent the median value of the strength of the temporal associations among symptoms. Dimensions 'lethargy' and 'Core (hypo)mania had the strongest out-strength levels, whereas 'somatic/suicidality' and 'dysphoric mania' the strongest in-strength.

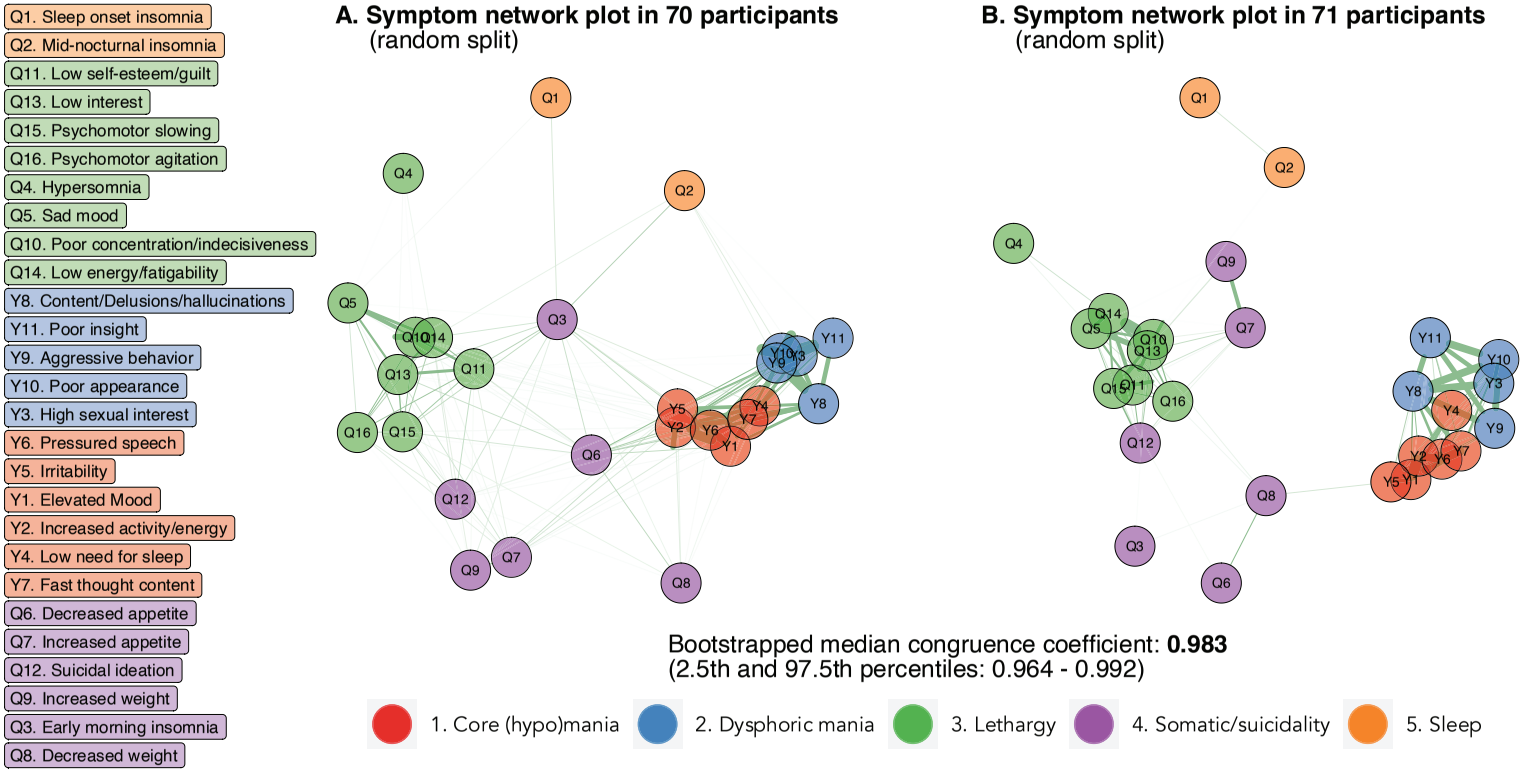


Figure 5.5: Network plots of two subsamples [A and B] of the 141 patients. We used an automated random split with a subset of 70 and 71 patients each, in which we conducted separate DTW analyses. Node placement was done by using the Procrustes algorithm (from the R Package 'networktools'), to aid the visual comparison between the two networks. The congruence coefficient through 200 random splits was high, with a median of 0.984 (2.5^{th} and 95^{th} percentiles: 0.967-0.993).

5.4 Discussion

The current study is the first to analyze a time series of depression and manic symptoms using DTW analyses in patients with BD. We studied interactions and relative changes in symptom severity within and between participants. Overall, the results of our individual patient analyses showed substantial variability between patients. Despite this individual variability, our group-level analyses revealed 5 symptom dimensions (core [hypo]mania, dysphoric mania, lethargy, somatic/suicidality, and sleep). The identification of these 5 symptom domains acknowledges the variability of clinical states that fall within the bipolar syndrome, which is much more complex than simply being either manic or depressed. The five symptom dimensions (core [hypo]mania, dysphoric mania, lethargy, somatic/suicidality, and sleep) that were identified through the group-level analyses, are robust since the clustering in two samples after a 200 random sample split-check analyses showed a large congruence factor. Moreover, we were able to analyze the temporal dynamics between these symptom dimensions as well. Below we will describe in more detail the clinical validity and implications of these findings.

The symptom cluster 'core (hypo)mania' seems to reflect the 'classical' manic state with increased energy, overactivity, and euphoric mood. This is in line with a recent network analysis showing that symptoms of core (hypo)mania were the most interconnected symptoms in the manic network.[30] The 'dysphoric mania' domain typically reflects what has previously been described as a mixed manic mood state,[31, 32] in which energy is high, but mood is characterized by irritation and agitation. Previous factor analyses also report both a 'pure' manic and a dysphoric factor[33, 34] in line with our findings. However, in the current study, the dysphoric domain also contains psychotic features. This specific combination resembles what Himmelhock, Coble, Kupfer, & Ingenito, 1976 described decades ago as an 'agitated psychotic depression in a small group of BD patients. The authors hypothesized that this psychiatric state represents a transitional period when the patient switches from depression to mania or vice versa but becomes 'trapped' in the 'switch' state. Also in a more recent review, it is implicated that approximately 20-30% of patients with BD may present mixed symptom states when transitioning from mania to depression or vice versa[35]. With the current data and analysis technique, we found evidence that this hypothesis might be correct. Indeed, the 'dysphoric manic state' seems to temporally follow the 'core (hypo) manic' mood state, implicating that the manic state tends to transitions into a mixed state over time. This also implies that the opposite direction could occur, when pure manic symptoms drop, dysphoric symptoms will drop subsequently. Clinically this means that in order to prevent a dysphoric state, manic symptoms should be diminished at an early stage. But also, once the patient is in a dysphoric state the interventions might preferably be anti-manic and not anti-depressant, in order to decrease the severity of the dysphoric state. This is in line with existing evidence that antidepressants (especially as monotherapy) during a mixed state could increase the severity of this state[36, 37].

Two other symptom domains that were found in our sample, seem to be positioned in the 'depressive pole', which are 'lethargy' and 'somatic/suicidality. 'Lethargy' consists of typical depressed symptoms (e.g., guilt, low interest, lack of energy, inactivity, hyposomnia). This seems to be in line with previous research, showing consistently 'sad mood' and 'low energy/fatigue' as the most central symptoms in depressive networks in

patients with BD[22, 23, 38, 39]. This domain also resembles the factor 'inhibited depression' as found by[40]. The 'inhibited depression' factor also typically lacked symptoms reflecting suicidality and was even associated with lower suicide rates. Similarly, in the current sample, suicidality falls into another cluster, in this case, the 'somatic/suicidality' dimension which importantly seems to overlap with the symptoms of a melancholic depression (changes in appetite, psychomotor slowing, early morning insomnia, and suicidality). The temporal dynamics between these dimensions in our an analysis shows that the 'lethargy' mood state with inactivity and feelings of guilt tends to precede increases in symptom severity in the somatic/suicidality mood state. Again, this also implies that decreases in the 'lethargy' domain tend to be followed by decreases in the somatic/suicidality domain, implicating that treatment might be focused on the 'lethargy' symptoms rather than 'somatic/suicidality' symptoms, in order to decrease the severity of either mood state.

Lastly, we found a separate insomnia domain in the current data, that appeared to be rather unrelated to the other mood domains. This is surprising, given the fact that sleep is such a central symptom of BD. A previous DTW analysis from our group also revealed a separate sleep dimension in patients with depressive episodes (Hebbrecht et al). This should not necessarily mean that sleep does not play an important role in bipolar disorder mood regulation, as it is possibly not specifically related to a specific mood state. Previous studies show that even during euthymia sleeping problems can remain present in a majority of the BD patients[41] which explains why sleep is not specifically related to the increase and decrease of the other symptom cluster in our sample. It might even imply that these symptoms are rather chronic in nature.

A major strength of the current study is that it provides insight in temporal dynamics of BD symptoms using time series, while many other clustering techniques focus on static cross-sectional analyses. It shows that DTW is a promising method that allows clinicians and patients to depict which change in dimension precedes that of which other dimension. It may help the clinicians in decision-making and personalized treatment. The individual-level analysis may eventually help to identify early warning symptoms of an episode in the treatment, when the number of assessments is large enough to detect consistent dynamics. The symptoms with the highest out-strength score could perhaps be targets in personalized treatment in order to prevent a more severe mood state. For instance, if a patient has central symptoms with the highest scores on 'early morning insomnia' and 'sad mood', these two symptoms could be primarily targeted in the intervention as these symptoms potentially could develop into other symptoms, resulting in a more severe episode. Another strength of this study is that we introduced individual-level as well as group-level analysis, whereas all previous studies analyzed static cross-sectional data on the group level only[42].

There are also some limitations that need to be discussed. The time intervals between assessments were long (3 to 6 months), and only up to 6 assessments were done per patient. Future studies could explore whether shorter intervals between assessments would yield similar symptom dimensions and centrality. Yet, many BD patients with a current episode may be incapable to complete daily or even weekly assessments. The co-occurrence of symptom dynamics that we have found in this study was however highly reliable among participants as illustrated by the high congruence factor and its tight confidence interact, and should therefore be considered as global BD symptom dimensions.

Finally, symptom scores are subjective, as they depend on the person's ability to correctly read their internal emotional states.

In sum, our patient-level analyses could be used to visualize a personalized profile of the dynamic relationship between the individual symptoms. This might help the clinicians and the patients to better understand individual patients' characteristic interaction of symptoms[43, 44, 45] A personalized approach might be important, as the idiographic findings tended to be highly variable between patients. DTW may be used for the detection of the central symptoms of one individual patient. Our group-level analysis underlines the variability of clinical states of the bipolar syndrome, which appears much more complex than the two poles of either mania or depression. Nevertheless, replication of the current study with shorter time intervals is recommended for future studies, in which also the influence of environmental factors could be incorporated (e.g., life events, changes in psychotropic medication, and lifestyle factors). Moreover, as we DTW analyses of symptom time series may only indicate only Granger causality, experimental designs are necessary to assess the clinical utility of targeting specific treatments at symptoms with high out-strength centrality. Whether patient-level analyses are of clinical value to more precisely target customized treatments should also be explored further.

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