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Clinical Network Analysis in a Bipolar Patient Using an Experience Sampling Mobile Health Tool: An n=1 Study

ALA Voigt[1], DJ Kreiter[1], CJ Jacobs[1], EGM Revenich[1], N Serafras[1], M Wiersma[1], J van Os[2-4], MLFJ Bak[2] and M Drukker[2*]

[1]*Faculty of Health Medicine and Life Sciences, Maastricht University, The Netherlands*

[2]*Department of Psychiatry and Psychology, School for Mental Health and Neuroscience MHeNS, Maastricht University Medical Centre, The Netherlands*

[3]*Department of Psychiatry, Brain Centre Rudolf Magnus, University Medical Centre Utrecht, Utrecht, The Netherlands*

[4]*King's College London, King's Health Partners Department of Psychosis Studies; Institute of Psychiatry, London, UK*

***Corresponding author:** Drukker M, Department of Psychiatry and Psychology, School for Mental Health and Neuroscience MHeNS, Maastricht University Medical Centre, The Netherlands, Tel: +31-43-3883913; E-mail: Marjan.Drukker@MaastrichtUniversity.nl

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Abstract

Objective: Analyses of longitudinal data pertaining to a single person can provide insight into the emotional dynamics of bipolar disorder at the symptom level. Aims were to examine (1) co-variation of a priori selected mental states in daily life in a patient with bipolar disorder; and (2) connections between these mental states during a hypomanic and a depressive period in bipolar disorder.

Methods: A single person diagnosed with bipolar disorder used the Experience Sampling Method (ESM) to collect data on experiences and mood ten times a day, for three months. Linear regression analyses were performed, stratified by hypomanic or depressive period. The a priori selected set of dependent variables included 'anxiety', 'down', 'cheerful', 'satisfied', 'tired' and 'lonely'. Independent variables were the same symptoms as collected one random moment earlier during the same day (t-1, lagged). Regression coefficients were presented in network graphs.

Results: Mood fluctuated strongly over time. The variable 'down' was central in the networks of both the hypomanic and depressive period. 'Satisfied' was only central in the hypomanic network.

Conclusion: In this patient, depression was the central emotion during both hypomanic and depressive periods. The distinction between depression and hypomania may sometimes lie in respectively the absence and presence of certain positive mood states. Furthermore, the present paper showed that extreme mood shifts in bipolar disorder can be studied after generating mood networks to gain precise insights in dynamic relations and the degree of cohesion between symptoms. These insights may be useful in the clinical setting to support self-monitored and personalised feedback and interventions.

Keywords: Bipolar disorder; Psychological networks; Psychopathology/methods; Ecological momentary assessment; Cluster analysis

Introduction

Bipolar disorder is characterised by two apparently contrasting periods: one with prominent manic symptoms and one with depressive symptoms. Although it is suspected that the different periods of bipolar disorder can be usefully represented as distinct networks of emotional states [1], little is known about the actual dynamic connections between emotions in depressed and hypomanic states.

Background

A person's mood is defined as an internally experienced sensation, affecting the way one perceives the environment. In a healthy person, fluctuations are common, causing mood to range from elevated to depressed [2]. Bipolar disorder is the vulnerability to experience extreme shifts in mood, with alternating periods of euphoric mood and periods of dysphoric mood. By studying networks in bipolar disorder or any other mental illness, using data at the level of momentary experience in daily life, as collected with the experience sampling method (ESM), insight can be gained into how mood variables dynamically relate to each other. This type of data, showing varying levels of connections between mood states in the network, can be usefully applied to support interventions based on self-monitoring and personalised feedback [3]. Given the contrast between hypomanic and depressive periods in bipolar disorder, it may be hypothesized that connections between mood states are also different across the two periods of mood alteration. In addition, it is plausible that the strength of the connections (centrality) also differs between the periods. When it is observed that the links of one symptom with various other symptoms are strong, the symptom is said to be more 'central' in the network. Insight in this phenomenon can be used to guide treatment [3]. For example, cognitive therapy can pay extra attention to symptoms that are central in the network and this can be different depending on the period of the illness.

ESM is a structured diary technique that is used to assess thoughts, moods, mental symptoms and context of subjects during the flow of daily life [3,4]. ESM has a high degree of ecological validity as it examines experiences in the real world as they occur naturally without interpretation by an interviewer [5,6]. The short time span between the experience and the actual reporting of the experience reduces memory bias and socially desirable answers [7]. The use of ESM over an extended period of time allows for the examination of person-specific variations and clustering of symptoms during daily life. In a previous n=1 clinical network analysis of a person experiencing psychotic symptoms, it was shown that meaningful patterns of symptom dynamics can be derived from the network and used in treatment. Recognition of person-specific symptom dynamics can thus empower patients to contribute to their own therapy in clinical practice [8].

Conventional research focussing on group-level comparisons is of limited value in the development of person-specific interventions, particularly in the area of mental health where extensive underlying heterogeneity between persons makes it difficult to derive signals from group-level comparisons [3]. Therefore, clinical network analysis using n=1 long-term ESM time series of experience and context are a valuable addition [8]. Clinical network analysis enables the clinician to analyse repeated observations without masking person-specific inter and intra-symptom associations.

In the present paper, a patient diagnosed with bipolar disorder gave informed consent to create a clinical network analysis using ESM data that the patient collected as a part of treatment. The patient used ESM seven days a week for a period of three months. This time span included parts of both a hypomanic and a depressive period. Data analysis is similar to a previous n=1 clinical network analysis in a patient diagnosed with psychotic disorder [8]. Out of the available set of mental states included in the ESM paradigm (appendix S1, in supporting information), the following were selected a priori, in consultation with the patient: 'anxiety', 'down', 'cheerful', 'satisfied', 'tired' and 'lonely'.

Aims of the Study

Analysis of these mood variables was used to answer the following research questions: (1) Do mood states co-occur and co-vary in a meaningful personal pattern over the observed three month period? (2) Does the strength of the connections between mood states vary in a meaningful manner with the emotional highs and lows in bipolar disorder? The present paper tries to contribute to the improvement of clinical care, not only for one patient, but also for similar patients that did not collect their own data.

Case Description

We refer to the participant as Mrs. M, aged 35 years and holding a bachelor's degree. She was diagnosed with bipolar disorder, type II in accordance with DSM IV. At the age of 22 years, she was admitted to hospital because of a hypomanic decompensation combined with paranoid thoughts. Since this time, she experiences severe mood swings that she finds very difficult to cope with. Early on over the course of her illness she attempted suicide four times. Various medication regimes and psychotherapy brought about some improvement in functioning but left the mood swings practically unaltered. Two years ago, she came under the care of the Flexible Assertive Community Treatment Team presenting the following problems: mood swings, feelings of hopelessness during depressive periods, requiring intensive home care and a difficult relationship with her (disapproving) mother. Her husband and in-laws are more supportive, having experience with bipolar disorder in the family (the husband's brother).

Mrs. M's mood states vary from hypomanic periods, during which she is able to cope reasonably well with life, enjoying high amounts of energy, to depressed periods, during which she struggles with daily activities, such as taking care of her daughter, and battles with suicidal thoughts, tiredly seeking refuge in bed. Within the macro-pattern of mood swings, there are micro-level, day-to-day and moment-to-moment variations in mood, which often are even more problematic, given their unpredictability and the ensuing sensation of loss of control. As she is afraid to become psychotic, and of having to be admitted again, she very much wants to remain in control of her experiences.

Mrs. M. has gained weight to the point of obesity (BMI 41 kg/m^2) and suffers from hypothyroidism which is supplemented with levothyroxine (50 µg/day). Her medication includes aripiprazole (5 mg/day) during hypomanic periods, and nortriptyline (25-50 mg/day) and lorazepam (2.5 mg/day) during depressive periods. Additional prescription medication includes lithium (1600 mg/day), promethazine (25 mg as necessary) and omeprazole (10 mg/day). These drugs may differ from guidelines because of continuous adaptation based on previous personal response in the course of Mrs. M's chronic illness.

During feedback sessions Mrs. M and her psychiatrist discussed frequency tables and associations of variables of main interest. This allowed her to gain more insight in daily symptom variation and offered possibilities of specific coping applications. The dominance of depressive feelings during the hypomanic period became undeniably apparent in such a manner that Mrs. M became willing to discuss this. She became more aware of her influence on symptom severity, which changed her attitude towards a more proactive coping approach as opposed to feelings of powerlessness regarding mood. The importance of other positive experiences gradually contributed to the realisation that she felt more uplifted on a daily basis than she was aware of. This experience corrected the general negative interpretation.

Method

Participant and informed consent

Mrs. M was not a participant in a study, but data were solely collected for treatment and made available for research afterwards. She provided informed consent for analysis of these data. As opposed to other ESM studies Mrs. M collected data for a relatively long period of three months. The study was approved by the IRB of the Institute for Mental Health Care Eindhoven and De Kempen (GGZE), Eindhoven, The Netherlands.

Instruments

Using a mobile Health (mHealth) application on her smartphone [3,9], Mrs. M was signalled ('beeped') ten times daily on various moments between 7.30 AM and 10.30 PM. With each beep, she was asked to answer questions regarding the nature and quality of experiences and mood. She answered these questions by rating her moods (for example feeling down) on a 7-point Likert scale between 1 ('not at all') and 7 ('very'). Furthermore, Mrs. M's psychiatrist (MB), with 19 years' experience, rated mood, affect, sleep and suicidality as part of routine outcome monitoring on 20 successive, standardised psychiatric evaluations, conducted during the period of investigation.

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Using these ratings, the psychiatrist identified two distinctive periods. In period 1, which ran from July 31st until September 14th 2015, Mrs. M's mood was clinically evaluated as hypomanic. In period 2, which ran from September 18th until October 26th 2015, her predominant mood was depressed. Using the data from the psychiatrist, MD replicated the moment of transition between period 1 and 2.

Statistical analysis

Statistical analyses were performed using Stata 13.1 [10]. Network graphs and centrality indices were obtained using R [11].

In order to analyse the first research question, mean scores per day were plotted for all a priori selected ESM mental states over time. Second, linear regression analyses were performed stratified by period. The dependent variables 'anxiety', 'down', 'cheerful', 'satisfied', 'tired', and 'lonely' were analysed in six separate models. The independent variables that were entered simultaneously in each of the six models were the same six mood variables measured at the previous beep in the ESM paradigm (lag or t-1) as well as a time variable. This yielded 36 coefficients per stratum, representing the strength of connections between the mental states over time. These regression coefficients were used to create two network graphs using the qgraph module [12] in R [11]. The nodes in these graphs represented mental states and the edges (connections) represent the regression coefficients. When a regression coefficients represents the association between an independent variable (at t-1) and the same dependent variable (at t) this association is called a self-loop.

Centrality indices were calculated using the R qgraph module [11]. However, because in lagged analyses the self-loop (between for example 'anxiety' at t-1 and 'anxiety' at t) is handled differently, node strength was obtained using excel. Centrality is defined as the sum of all inward and outward connections; conform previous work, the self-loop was counted twice [8]. Closeness is another measure of centrality, indicating how close a node is to other nodes (inverse of the strength) using the shortest path.

Results

During the 90 days of data collection, Mrs. M answered 447 beeps (49.7%). The response was higher in the hypomanic period (52.6%) compared to the depressive period (44.4%; RR=1.19; 95% CI 1.03-1.37).

Mood levels over time

Figure 1 illustrates fluctuations of mood during both the hypomanic and depressive periods, indicated by the green and red horizontal lines, respectively. There was a clear distinction between the periods. In addition, all mood variables showed a strong day-to-day variation, except for 'lonely'. This mental state only shows stronger peaks during the depressive period. As expected, 'down' was most elevated during the depressive period. The solid lines at the beginning of the depressive period represent an interval during which Mrs. M temporarily stopped rating her moods.

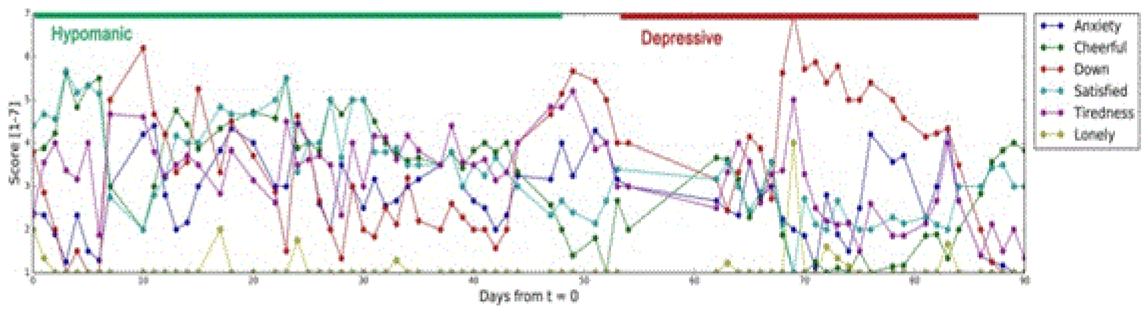

Figure 1: Variability of mood states over time during the hypomanic and depressive period.

Mood networks

Mood networks of the hypomanic and depressive period, respectively, are presented in Figures 2 and 3. In the hypomanic period, 'satisfied' was dominant, in combination with 'down'. Both mental states had a strong positive self-loop, and 'down' showed a strong negative association with 'satisfied'. In the depressive period, 'satisfied' was no longer central and the level of fluctuation of 'cheerful', 'tired' and 'anxiety' was lower than in the hypomanic period. 'Down', however, was still central in the depressive period. Even though absolute scores of 'lonely' showed a peak during the depressive period, it was more central in the hypomanic period.

The node strength of all mood variables, except for cheerful, was lower during the depressive period (Table 1). The node strength of the mood variables 'tired', 'anxiety' and 'cheerful' was similar across both periods. Both 'down' and 'satisfied' were prominent in the hypomanic period (higher levels and higher node strength than the other symptoms). In the depressive period, the prominence of 'satisfied' was greatly reduced while levels of 'down' remained high and it was the only central symptom. Closeness did not differ between the symptoms and was similar across both periods. When assessing overall network strength (connectivity), there was very little difference between the hypomanic and the depressive period (5.16 and 6.25, respectively). Differences in centrality between the periods were not tested because clinical relevance was deemed more important.

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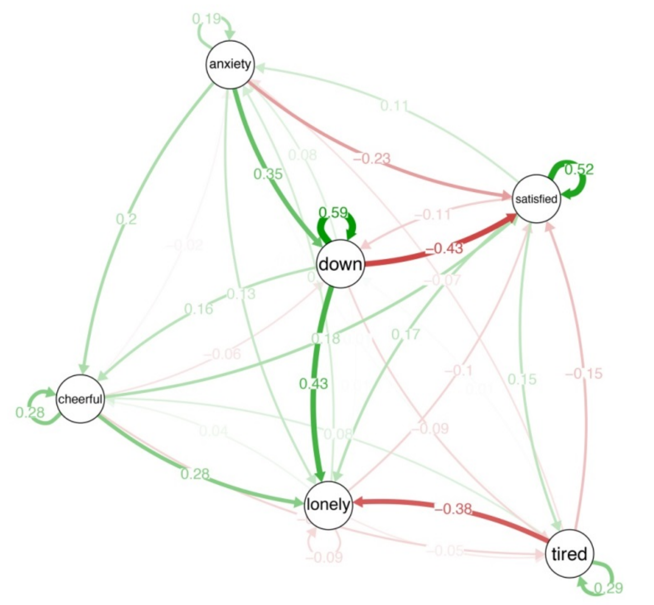

Figure 2: Network of a priori selected mental states in a bipolar patient (hypomanic period).

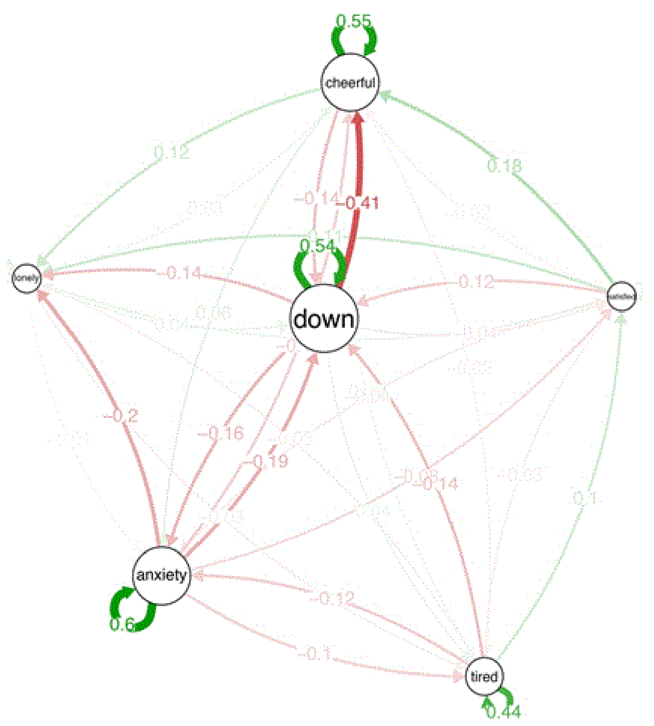

Figure 3: Network of a priori selected mental states in a bipolar patient (depressive period).

Mood variables	Node strength	Closeness
Period 1: Hypomanic[a]		
Cheerful	1.42	0.02
Satisfied	2.16	0.02
Lonely	1.78	0.02
Tired	1.38	0.02
Anxiety	1.49	0.03
Down	2.33	0.03
Period 2: Depressive[a]		
Cheerful	1.66	0.01
Satisfied	0.83	0.02
Lonely	0.82	0.01
Tired	0.99	0.02
Anxiety	1.67	0.03
Down	1.97	0.02

Table 1: Centrality indices.

[a] Connectivity, defined as the sum of absolute values of all coefficients between variables, was 5.16 in period 1 and 6.25 in period 2.

Discussion

Mental states experienced by a single person with a diagnosis of bipolar disorder were analysed over a period of three months. Reported absolute mood scores fluctuated widely over time. Nonetheless, clinically observed predominantly hypomanic and depressive periods were clearly distinguishable from one another. 'Down' and 'satisfied' played a prominent role in the network of the hypomanic period, as indicated by their centrality indices. In the depressive period, the prominence of 'satisfied' was greatly reduced and 'down' persisted as the most central symptom.

Comparison of results with literature

The finding that 'down' had the highest node strength centrality in the depressive period of bipolar disorder is consistent with earlier work in depressive disorder [13]. In the same paper, the node strength of 'satisfied' was relatively low in patients with depression. This finding corresponds with 'satisfied' in our bipolar patient during the depressive period.

The most important finding in the mood networks was the inter-period variation in the presence of the mood variables 'down' and 'satisfied', as well as their centrality. Satisfied was only central in the hypomanic period, while down was central in both periods. 'Down' and 'satisfied' are items assessing negative affect and positive affect, respectively. Negative affect is a general factor of subjective distress and subsumes a broad range of negative mood states, whereas positive affect reflects the person's level of pleasurable engagement with the environment. Depression has been shown to be a mixed state of high negative affect and low positive affect [14,15]. It is elicited by a lack of contingent positive reinforcement [16]. The depressed individual receives less positive reinforcement as a result of a lower activity level, a restricted range of activities and a decrease in reinforcement potential [16]. In patients diagnosed with depression, high levels of positive affect have been associated with a better course of illness; positive affect was on the causal pathway between treatment and favourable depression outcomes [17,18]. The observation of fluctuations in positive affect in subjects combined with a relatively stable report of negative affect strengthens the idea that it is in fact a change in positive affect which may underlie the emergence of depression [15]. In other words, positive affect may dominate negative affect in manic or hypomanic periods, allowing the patient to effectively cope with these negative experiences. This is supported by work dating back to the beginning of the 20th century stating that mania is an attempt to cope with depressive mood [19]. This theory is in agreement with the current finding that it is not the presence and the central place in the network of depressive mood, but rather the absence or non-central role of positive affect that marks the difference between the depressive and hypomanic period. Insight in ESM-based mood networks may aid treatment, as previous research showed that ESM-derived feedback on positive affect results in a lasting decrease in depressive symptomatology [20].

Implications and Treatment

The finding that satisfaction makes the difference between the depressive and the hypomanic period means that even in the hypomanic period, depressed feelings are present and central. While the concept of 'mixed' states is well-known, the results in fact suggest that (subtle) states of mixed affect may be the norm rather than the exception. As far as we know, the present paper is the first to show that depressive symptoms can be both present and central during a hypomanic period. Addressing these depressive symptoms during this period of bipolar disorder could improve treatment. More research is necessary to learn whether similar patterns exist in other patients. After replication, patients that did not collect their own ESM data can also benefit when discussing patterns in patients with a similar diagnosis.

Feedback using individual ESM data focussing on positive affect has been associated with decreases in depressive symptoms [20] and, thus, may serve to neutralise negative affective states. Based on the present results and results from a previous n=1 study [8], we may conclude that the prolonged use of ESM can help in treatment. Additional information of ESM derived networks increases insight in the interplay between symptoms. In bipolar disorder, mood swings are common, but they may not be anticipated by the patient. The advantage of the use of ESM over a prolonged period is that symptom changes that represent the personal dynamics of the disorder can be visualised and discussed with the patient [4]. Standard psychometrics such as questionnaires, have a time frame of, for example, the last 2 weeks and, thus heavily depend on intact cognitive functioning. To both remember and simultaneously judge the severity of a symptom over the last 1 or 2 weeks is difficult, because symptoms change continuously. Long-term ESM follow-up enables a patient to become more aware of the severity and personal dynamics of symptoms. Thus, changes over time as reported by the patient reveal fluctuations that otherwise would not have come to the fore. This insight can help to start personalised interventions. For Mrs M, these interventions would differ between the hypomanic and the depressive periods.

Methodological Issues

The strength of the present paper is the high number of ESM observations in one patient (n=1), creating the intensive time series required for clinical network analysis. This provided important findings that were not obscured by inter-person variability. Because of the single-patient design, symptoms of one patient were compared over time; between-person comparisons of symptoms were not performed. The higher order goal of this work is to show proof-of-principle of clinical network analysis in clinical practice, where all treatment is essentially person-specific given extensive heterogeneity between patients in all aspects. The design thus enabled us to find important associations between symptoms that might have been missed in a between-person comparison [21].

In addition, the real-time data collection strategy offered ways to reduce the effect of recall bias and provide a better assessment of the patient. Individuals are more likely to recall or report experiences that seem more personally relevant, occurred more recently, stand out as significant or unusual, or are consistent with their current mood state. These sources of error that are inherent in many traditional assessment techniques were avoided with the use of ESM [22]. However, ESM also has limitations. First, a disadvantage of the n=1 design is that results are fundamentally only applicable to the individual studied [23,24]. On the other hand, patterns more easily remain obscured when analysing data of multiple patients. Analysis of single patient data is an addition to studies assessing multiple subjects. Both types of research complement each other.

Using ESM for several months requires considerable time and commitment. Because of self-selection bias only those who are motivated, willing to volunteer and willing to complete a data collection, are included in this type of research. However, ESM is feasible for a large subgroup of the patients because, currently, the use of a smartphone is common and the mHealth app nicely fits in [7]. In addition, compliance is simplified as patients become familiar with the fixed content of the questions. Therefore, Mrs M can be seen as representative for a large subgroup of patients.

The 49.7% answered beeps are similar to response in a patient diagnosed with psychosis [8]. In general population samples, respondents miss approximately one third of the beeps [7]. Most beeps are missed because of valid reasons, for example sleeping in the morning [7,25]. Thus, answered beeps are representative for every moment a participant is able to answer the ESM questions. The higher loss of response in n=1 studies can be a consequence of the duration of data collection (Mrs. M three months). In addition, response may be lower in psychiatric patients, which may have led to more selective loss of data than in healthy patients. Nevertheless, the information obtained was substantial. As could have been expected, response was slightly higher in the hypomanic period. Because differential non-response is not expected, wrong representation of the networks is unlikely.

Second, it is well-known that ESM assessments may induce participants to reflect on their responses and that this may lead to changes in their behaviour [6]. In ESM studies, researchers try to prevent this by briefing the participants, because it interferes with the study. Mrs. M collected data for her treatment. Reflecting and changes in her everyday life were the reason that ESM was used in treatment. Although this makes the data less ideal for research, results from n=1 ESM studies form valuable information because data is collected over a longer period of time.

Third, in between the hypomanic and depressive period there was a small time frame of eight days during which no ESM data was collected (Figure 1). According to her psychiatrist, Mrs. M simply did not feel like answering the ESM questions during this period. These days match the transition from hypomania to depression. A network of this transition phase would have been highly relevant. Nevertheless, analyses of both periods separately without the transition also provided relevant information. To study this transition period, additional ESM assessments in other participants are necessary.

Furthermore, analyses showed that most connections in the networks in both strata were not statistically significant. However, they were presented and described because of possible clinical relevance. Figure S1 (in supporting information) presents network graphs showing exclusively statistically significant connections. Statistical analyses to compare the two networks could have been a valuable addition to the present results. However, standard statistical analysis techniques are invalid for these comparisons because variances of the dependent variables differ between the periods and in our opinion time-consuming permutations are beyond the scope of the present paper. When including interaction terms between period and the independent variables in the regression models, despite the possible flaws, the associations between cheerful and down, satisfied and down and the self-loops of satisfied and anxious differed between the hypomanic and the depressive period. Post hoc, the full set of mental states included in the ESM assessment was analysed (as opposed to the a priori selected variables in the main analysis). Figure S2 (in supporting information) present networks obtained from those analyses. Despite the higher number of nodes, conclusions were the same as in the main analyses.

Finally, during the period of data collection, Mrs. M experienced a hypomanic and a depressive period, but was never euthymic. Therefore, it was not possible to create a 'control' network. A comparison between a euthymic period and a depressive period or a hypomanic period would have been valuable. Euthymic data should be included in future data analysis.

Conclusion

In this patient, satisfaction as a positive mood item was present in the hypomanic period. Because down was present and central in both the hypomanic period and the depressive period, satisfaction was the factor that discriminated between the periods. More research is needed to examine to what degree this finding is unique for this particular patient or more broadly representative of all patients. Understanding the difference between depression and hypomania as the absence and presence of certain positive mood states, can help to develop personalised interventions.

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