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Is symptom connectivity really the most important issue in depression? Depression as a dynamic system of interconnected symptoms revisited

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ABSTRACT

According to the network theory strong associations between symptoms drive the disease process. We compared those with and without diagnosed depressive disorders (DD+/DD-) and analysed the effects of differences in (a) network connectivity, (b) symptom thresholds, and (c) autoregressive loops (i.e. how strongly specific symptoms predict themselves) on the potential activation of symptoms over time using simulations developed by Cramer and others (2016). The parameters for the simulation (symptom connectivity and symptom threshold) were obtained from Ising models and cross-lagged panel network analyses. Data were from the nationally representative samples (Health 2000–2011 Study) of 4190 participants measured in 2011 (cross-sectional analyses) and 3201 participants measured in 2000 and 2011 (longitudinal analyses). DD diagnosis was based on the Composite International Diagnostic Interview and depressive symptoms were self-reported using the 13-item version of the Beck Depression Inventory (BDI). Differences in symptom connectivity between participants with and without DD were not observed, but the mean probability (threshold) of symptom existence in the DD + group was higher than in the DD-group (0.41 vs. 0.12). Simulation showed that there are more active symptoms in the DD + group after 10 000 time points (means 1.2 vs. 4.6) than in the DD-group. This difference largely disappeared when we used longitudinal networks, including autoregressive loops, in the connectivity matrix. Our results suggest that the differences in symptom thresholds and autoregressive loops may be more important features than symptom connectivity in differentiating people with and without DD.

1. Introduction

The network theory of psychopathology postulates that mental disorders consist of individual symptoms that are causally related (Borsboom, 2017; Cramer et al., 2016; Fried and Cramer, 2017) and that strong relations between symptoms make individuals vulnerable to mental disorders (Chen et al., 2000; Djelantik et al., 2020; Fried and Nesse, 2015a; Fried et al., 2016; Robinaugh et al., 2020). In studying mental disorders, such as depression, there are multiple good theoretical justifications for this idea. It is, for example, reasonable to assume that poor sleep causally affects activity levels and concentration, and heterogeneity of the symptoms in depression does not support the common cause idea. Multiple empirical findings showing that different depression symptoms are related to different risk factors (Fried et al., 2014) and different patterns of comorbidity (Lux and Kendler, 2010), causing different levels of impairment (Fried and Nesse, 2015b; Fried et al., 2015), also support the network theory. This kind of conceptualization suggests that the central disease mechanism for depression is the spread of activation of individual symptoms in a causal network (Borsboom, 2017; Cramer et al., 2016). The individual symptoms, once they are activated, affect and activate other symptoms, and if individuals have a specific architecture of symptom relations and strong connections between symptoms, they may be at higher risk of contracting a systemic state of symptoms that previous studies have called an emergent attractor state: 'depression'. Such a disease state is formed by vicious circles of mutually affecting symptoms that can be difficult to break (Cramer et al., 2016). In addition to empirical studies mostly based on clinical samples (Boschloo et al., 2016; Bringmann et al., 2015; Cramer et al., 2016; Fried et al., 2016; Fried et al., 2016; van Borkulo, Boschloo, Borsboom, & al., 2015), the simulations study by Cramer and others

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(2016) using estimates from a population-based sample showed that by manipulating network connectivity in a depressive symptom network it was possible to predict the number of symptoms over time. Stronger associations between symptoms predicted more future symptoms and even the inability to return to the state of no or only few symptoms.

Although the connectivity hypotheses postulated by the network theory of mental disorders have been supported (Robinaugh et al., 2020), some important issues remain unresolved or insufficiently clarified. First, recent large-scale empirical studies have not been able to offer strong support for the connectivity hypothesis. A recent study using partially the same data as the current study showed that participants with diagnosed depression did not have stronger symptom connectivity (Hakulinen et al., 2020). Similarly, a study using the Health and Retirement Study revealed that stressful life events, such as receiving a cancer diagnosis, did not increase symptom connectivity (Airaksinen et al., 2020). In addition, adolescents with depression who continued to experience symptoms did not have more densely connected networks at baseline than patients who later recovered (Hakulinen et al., 2020; Schweren et al., 2018). Second, most of the studies have been conducted either with patients or with community samples and have therefore not been able to compare depressed individuals with healthy ones within the same dataset or with measures that are independent of symptoms evaluated as a network. Third, it is obvious that people with depressive disorder (DD) have more symptoms than those who without DD, because in most studies the severity of DD is measured by the number of symptoms. It is suggested that the more frequent symptoms may be caused by more external forces, such as stressful life events or lower threshold of resisting these forces or both (Kendler and Gardner, 2016; Kendler et al., 2004). The lower threshold of resisting external forces in network literature have been referred to as the "tipping point" difference (Cramer et al., 2016), meaning the critical threshold at which a perturbation (such as stress) can alter the state or development of an individual or multiple symptoms. Through spreading of the activation of the symptoms in the connected network may then alter the state of the entire system. The association between the network connectivity and the level of symptom threshold, however, remains somewhat unclear and it is not reasonable to assume that the lower threshold of experiencing symptoms is an inevitable result of a higher connectivity.

In addition to these shortcomings, some theoretical justifications may be slightly problematic. It may be reasonable to assume that sleeping poorly is associated with fatigue and concentration problems in everyone and not just in those who will develop depression or depressive state. Perhaps some people just sleep well the next night and others keep on sleeping badly, consequently developing the systemic state that we call depression. Thus, it may be that there are differences in the strength of the feedback loop within symptoms between those who will develop depression and those who will not. The last two points were not addressed in the original paper by Cramer and others (2016) because they were unable to model differences in thresholds and they did not evaluate the autoregressive associations within symptoms.

To examine the potential effects of symptom connectivity, symptom threshold, and autoregressive loops on symptom activation over time, we analysed the data from a large representative sample (Health 2000–2011 Study) of 4190 participants from Finland. We estimated the network structures, symptom connectivity, symptom predictability, and symptom thresholds in participants with and without DD. In addition, we used the algorithm developed by Cramer and others (2016) to test whether these differences would predict a different number of potentially activated symptoms in these groups. Last, we examined whether adding autoregressive loops estimated from the cross-lagged network models (Rhemtulla et al., 2020) to the networks would change the prediction of activated symptoms. We thus, wanted to analyze, whether the core assumption in psychological network theory, that specifically the strong relations between symptoms make individuals vulnerable to mental disorders, or are the symptom thresholds really more important for development of depressive symptoms.

2. Materials and methods

We used both cross-sectional and longitudinal data derived from the multidisciplinary epidemiological survey - the Health 2000–2011 Study that was carried out in Finland in 2000–2011 (Koskinen et al., 2011). In 2000 (T1), a nationally representative sample was drawn among adults aged 30 years or over and living in the mainland of Finland. Two-stage clustered sampling of 15 largest towns and 65 health districts in Finland was used and individuals over 80 years were oversampled (2:1). In addition, young adults' sample of individuals who were between 18 and 29 years old were collected using shortened version of the study protocol. In 2011, all participants who were alive, living in Finland, and had not refused to participate, were invited to take part of new data collections wave (T2).

In Health 2000), a total of 7419 participants (93% of the invited subjects alive) participated to the study. Of these, 6005 participated in the clinical examination, which included, e.g., the Composite International Diagnostic Interview (CIDI), which was reliably performed (75% of the original sample). In Health 2011), a total of 4246 participated in the health examination. The participants were restricted to those who had undergone a diagnostic interview and responded to the depression questionnaire and in the final analyses sample for the cross-sectional analyses with complete data included 3905 patients without DD and 285 patients with DD measured in 2011. For the longitudinal analyses, data from 2000 to 2011 were used. The data included 2836 men and women without DD in 2000 and 2011 and 365 with data on DD in 2000 or 2011.

The mean age of participants in the total population was 48.6 years (SD = 19.1 years) and 40% had applied or university degree education. Those in DD + group were slightly younger (49 vs. 55, $p < 0.001$) and more often women (8.5% vs. 4.5%, $p < 0.001$) but there were no differences in the educational attainment.

2.1. Diagnoses

Depressive disorder diagnoses were based on the Composite International Diagnostic Interview (M-CIDI (Wittchen and Pfister, 1997), using operationalized criteria for DSM-IV diagnoses, allowing an estimation of DSM-IV diagnoses for mental disorders. The interviews were performed to determine the 12-month prevalence of depression (dysthymia or major depressive disorder, MDD). The interrater reliability was good (Pirkola et al., 2005b).

2.2. Depressive symptoms

Depressive symptoms were assessed using the 13-item Beck Depression Inventory (BDI) (Beck and Beck, 1972; Beck et al., 1961). Due to non-normal distributions, depressive symptoms were dichotomized (0 = no symptoms, 1 = any other option). BDI -13 was used because it is one of the widely used scale that also includes all depressive symptoms defined by the Diagnostic and Statistical Manual of Mental Disorders 5 and have also shown to have good psychometric properties (Aalto et al., 2012).

3. Statistical methods

3.1. Network characteristics estimation

Network structures of cross-sectional depressive symptoms were estimated in participants with and without DD in 2011 using the IsingFit R-package, which uses Lasso regularized logistic regressions and Extended Bayesian Information Criteria and provides weights (basically regression coefficients) between symptoms and symptom thresholds (intercepts) that can be changed to probabilities of being 1. Thresholds may be described regarding the extent to which a symptom has a preference to be "on" or "off". A threshold of 0 means that a symptom has no

preference, while a threshold of higher or lower than 0 indicates that a symptom has a certain probability for being "on" or "off", respectively. Predictability of each symptom was calculated using the mixed graphical model (MGM) and mgm package (Haslbeck, 2016). Potential differences in overall and local connectivity between participants with and without DD were examined using the two-tailed permutation NetworkConnectionTest (NCT) R-package (Van Borkulo, 2015), with repeated (100 000 times) calculations of randomly regrouped individuals. The longitudinal symptom network was estimated using the cross-lagged network modeling presented by Rhemtulla and others (2020). We estimated logistic regression coefficients of each variable at T2 (year 2011) on itself and all other variables at T1 (year 2000). Regression coefficients were estimated using penalized maximum likelihood with a Lasso penalty on the estimated regression coefficients (Friedman et al., 2010). This estimation technique has the effect of shrinking small regression paths to exactly zero, while making other paths larger. These regression analyses were done using the glmnet R-package.

Edge weight stability and the accuracy of the order of centrality were explored using procedures recommended by Epskamp et al. (2018).

3.2. Simulation

An algorithm for "the formal dynamic systems model" of major depression (MD) developed by Cramer and others (2016) was used to build a dynamic intra-individual model of MD, based on the estimated weight and threshold parameters in DD+ and DD-groups, which develop over time. The main characteristic of the model is that the activation of a symptom influences the probability of activation of other connected symptoms. Simulating data with this model gives us an opportunity to test whether these two parameters (connectivity/weights between symptoms and symptom thresholds) produce more or less symptoms over time, i.e. with the subject being more or less likely to develop a depressed state, respectively. Applying this formal dynamic system model, we additionally examined whether using longitudinal associations, including autoregressive feedback loops, would affect the development of depressed state of the network.

Although the algorithm for the formal dynamic system model of MD is well presented in Cramer and others (2016), we will briefly outline it here. The model proceeds in the following steps: The total amount of activation a symptom receives at time t is assumed to be the weighted summation of all active neighboring symptoms (i.e. 0 and 1 values at time t – 1), which is called the total activation function. A logistic function is then used for computing the probability of a symptom becoming active at a given time, and the probability of a symptom becoming active at the same time depends on the difference between the total activation of its neighboring symptoms and the threshold of that symptom. The more the total activation exceeds the threshold of a symptom at a given time, the higher the probability that the symptom becomes active. The model is an intra-individual model that develops over time. Unlike in the original study, we used the connectivity estimates, thresholds, and autoregressive associations estimated from the data for the DD- and DD + groups.

All statistical analyses were conducted using R 3.6.1 (R-Core Team).

4. Results

4.1. Cross-sectional analyses

Individual depression symptoms for participants with and without DD are shown in Table 1. Significant differences emerged in the average amount of symptoms between the two groups (people with DD had a higher level in all individual symptoms, all p-values were <0.001). The visualization of the networks for the DD- and DD + groups and the symptom predictabilities are presented in Fig. 1. The associations (weights) are illustrated as edges between the nodes (symptoms) such that thicker edges are stronger associations and the predictability of each symptom is illustrated by the percentage of shaded area in the pie. The symptom predictability was lower in the DD-group than in the DD + group (mean predictability in DD- 0.18 and in DD+ 0.49) although there are no ways to calculate the statistical significance of the difference. Due to differences in sample sizes we calculated the average predictability also in five smaller random subsamples (n = 300) from DD-sample and all mean predictabilities were quite similar (0.237, 0.176, 0.208, 0.218, 0.209) to compete DD-sample. The network in DD-group was quite stable and accurate (SFigure 1 – SFigure 3). The stability coefficient for the strength centrality was 0.75). The network in DD + group was also relatively stable despite the smaller sample size (SFigure 4 - SFigure 6) and stability coefficient for strength centrality was 0.59.

Table 1
BDI depressive symptoms according to CIDI-diagnosed depressive disorders (No = DD- and Yes = DD+).

BDI symptom		DD-	DD+	p-value
	N (%)			
Sadness	No	3577 (91.6)	129 (45.3)	<0.001
	Yes	328 (8.4)	156 (54.7)	
Pessimism	No	3747 (96.0)	190 (66.7)	<0.001
	Yes	158 (4.0)	95 (33.3)	
Past failure	No	3574 (91.5)	170 (59.6)	<0.001
	Yes	331 (8.5)	115 (40.4)	
Loss of pleasure	No	3600 (92.2)	150 (52.6)	<0.001
	Yes	305 (7.8)	135 (47.4)	
Guilty feelings	No	3269 (83.7)	115 (40.4)	<0.001
	Yes	636 (16.3)	170 (59.6)	
Self-dislike	No	3612 (92.5)	167 (58.6)	<0.001
	Yes	293 (7.5)	118 (41.4)	
Suicidal thoughts	No	3582 (91.7)	155 (54.4)	<0.001
	Yes	323 (8.3)	130 (45.6)	
Loss of interest	No	3363 (86.1)	153 (53.7)	<0.001
	Yes	542 (13.9)	132 (46.3)	
Indecisiveness	No	3216 (82.4)	125 (43.9)	<0.001
	Yes	689 (17.6)	160 (56.1)	
Worthlessness	No	3384 (86.7)	160 (56.1)	<0.001
	Yes	521 (13.3)	125 (43.9)	
Loss of energy	No	3082 (78.9)	127 (44.6)	<0.001
	Yes	823 (21.1)	158 (55.4)	
Tiredness or fatigue	No	2148 (55.0)	70 (24.6)	<0.001
	Yes	1757 (45.0)	215 (75.4)	
Change in appetite	No	3727 (95.4)	232 (81.4)	<0.001
	Yes	178 (4.6)	53 (18.6)	

In Fig. 2, the same networks are presented, but this time the thresholds for firing the individual symptoms as "on vs. off" converted to probabilities are illustrated as the percentage of shaded area in the pie. In the DD + group, the symptom probabilities were consistently higher (average probability in DD + group 0.17 and in DD-group 0.05) than in the DD-group.

However, according to the Network Comparison Test, no differences existed in overall structure (p = 0.97) or connectivity (p = 0.53). The only significantly different associations were between symptoms 5 and 1 (p = 0.04), between symptoms 5 and 11 (p = 0.04), and between symptoms 11 and 13 (p = 0.04). However, when considering the multiple testing, none these differences are significant after Bonferroni corrections and thus probably not robust.

Because we used a community sample the sample sizes in DD- and DD + groups were naturally quite different and the finding that there were no differences in connectivity between the groups could be due to the smaller sample size of the DD + group and because the power to detect an edge is lower, the network could be less dense. However, we conducted as sensitivity analyses, the NCT with five random samples (n = 300) from the DD-group and detected the same results. Test statistics M-values and p-values for the network structure difference test were 1.18, 1.39, 2.18, 1.68, 1.41 and 0.83, 0.55, 0.06, 0.21, 0.47 respectively. S-values and p-values for the global connectivity difference test were 3.89, 2.47, 5.74, 5.30, 5.78 and 0.35, 0.50, 0.18, 0.20, 0.12 respectively

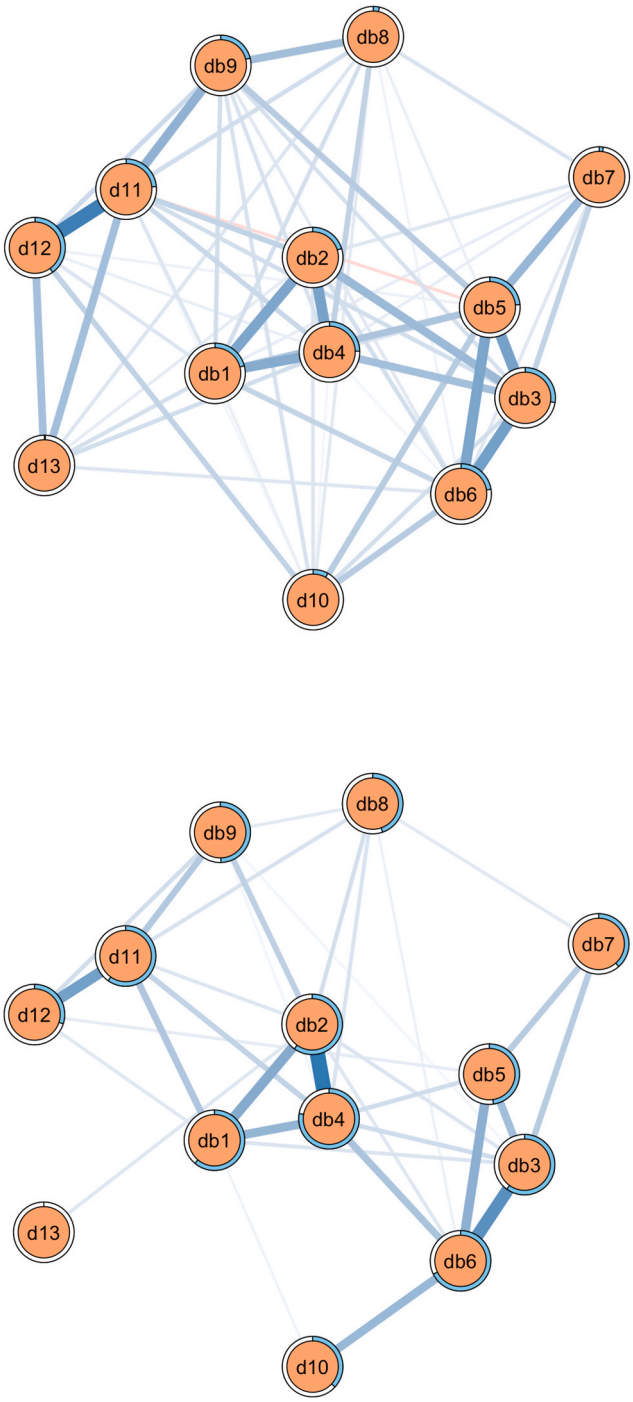

Fig. 1. Visualization of cross-sectional networks for DD- (above) and DD+ (below) participants. The pie share is the predictability of the symptom.
b1 = Depressed mood/sadness
b2 = Pessimistic about the future
b3 = Low self-esteem/past failure
b4 = Loss of pleasure/dissatisfaction
b5 = Feeling guilty
b6 = Feeling disappointed in oneself/self-dislike
b7 = Self-harm
b8 = Losing interest in other people
b9 = Difficulties in decision-making.
b10 = Dissatisfaction with one's appearance/worthlessness
b11 = Work disability
b12 = Tiredness
b13 = Loss of appetite.

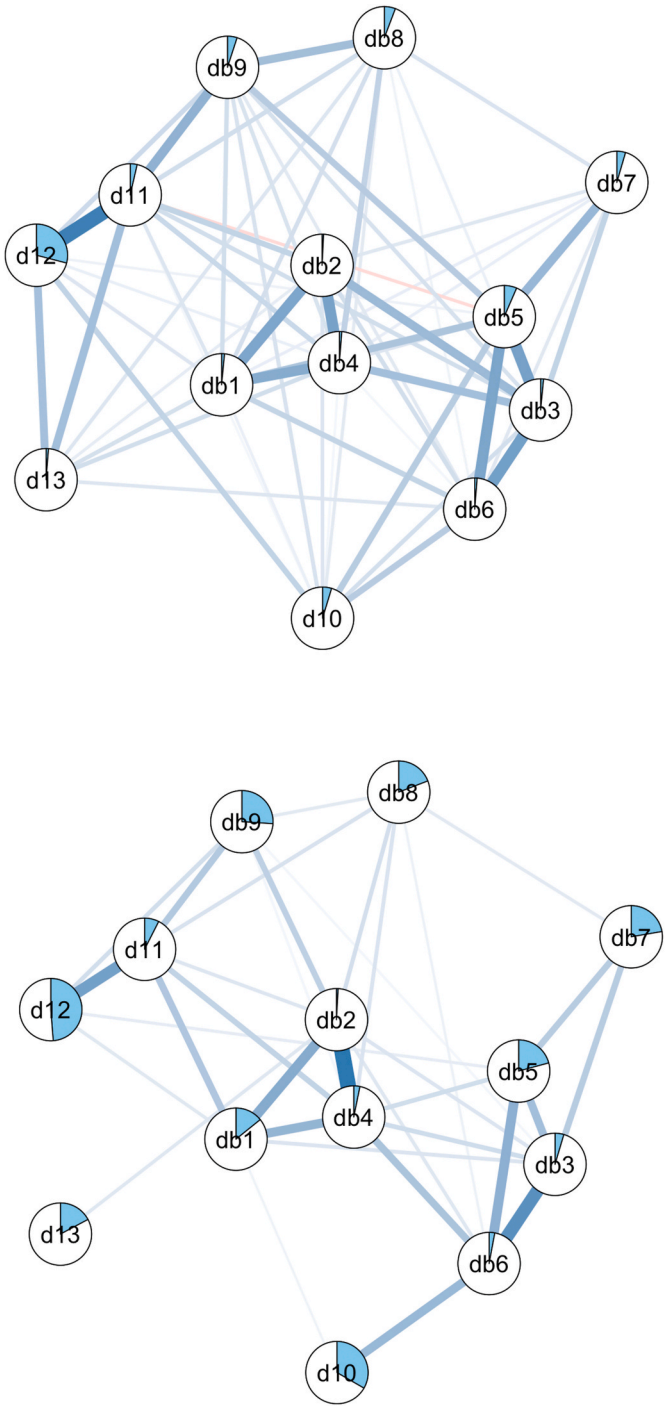

Fig. 2. Visualization of cross-sectional networks for DD- (above) and DD+ (below) participants. The pie share is the probability of the symptom to be "on".
b1 = Depressed mood/sadness
b2 = Pessimistic about the future
b3 = Low self-esteem/past failure
b4 = Loss of pleasure/dissatisfaction
b5 = Feeling guilty
b6 = Feeling disappointed in oneself/self-dislike
b7 = Self-harm
b8 = Losing interest in other people
b9 = Difficulties in decision-making
b10 = Dissatisfaction with one's appearance/worthlessness
b11 = Work disability
b12 = Tiredness
b13 = Loss of appetite.

(see also Supplement).

The results of simulation function based on the network parameters (the dynamic system models) in DD- and DD + are shown in Fig. 3, where the y-axis shows how many symptoms are activated and the x-axis shows the number of simulated time transitions, based on the estimated network connectivity and symptom thresholds in DD- and DD + groups. In the DD-group, the number of activated symptoms stays relatively low the whole time (mean number of activated symptoms over simulated time points was 1.2), but in the DD + group the variation is much larger and the number of activated symptoms over simulated time points was on average higher (4.9) than in the DD-group.

4.2. Longitudinal analyses

Fig. 4 shows the cross-lagged panel networks (from 2000 to 2011) as directed networks among the DD- and DD + groups. All arrows represent cross-time effects. The arrow thickness represents the strength of the effects and color represents the direction of the effect (green arrows represent positive effects and red arrows negative effects). Similarly to cross-sectional networks, the longitudinal cross-lagged panel networks did not differ between DD- and DD + groups. Only a few significantly different associations existed between the groups, and only three of them were in the autoregressive associations. In fact, pessimism ($p = 0.04$), loss of energy ($p = 0.02$), and change in appetite ($p = 0.01$) had stronger autoregressive associations in the DD-group than in the DD + group.

The results of the dynamic system models using the longitudinal associations including autoregressive loops in DD- and DD + are presented in Fig. 5, where again the y-axis shows how many symptoms are activated and the x-axis shows the number of simulated time transitions based on the estimated longitudinal network connectivity and symptom thresholds in DD- and DD + groups. In the DD-group, the number of activated symptoms stays again relatively low the whole time (mean number of activated symptoms was 1.03), and again in the DD + group the variation is somewhat larger and the number of symptoms is on average (mean number of symptoms 3.00) higher than in the DD-group. However, these differences were much smaller than in the models using cross-sectional associations.

5. Discussion

Using nationally representative data from Finland, we examined differences in depressive symptom network connectivity and symptom thresholds, and tested the potential effects of differences in (A) depressive symptom connectivity, (B) symptom threshold, and (C) autoregressive loops on symptom activation in participants with and without DD. In other words, we tested whether differences exist between depressed and non-depressed individuals in how strongly specific symptoms are connected to other symptoms, how easily the symptoms are triggered in response to other symptoms, and whether specific symptoms are associated with strengthening of the same symptoms over time (autoregressive effects). We simulated the symptom activation by using the formal dynamic systems model of MD developed by Cramer and others (2016). Our results showed that symptom connectivity was not higher in participants with depressive disorder than in those without. However, the symptom thresholds were clearly lower in the DD group, which means that the symptoms are more easily aroused in response to changes in the environment in depressive versus non-depressive participants. Individual symptoms also affected the average number of activated symptoms over time more strongly in depressed than non-depressed participants. Repeating the analyses using longitudinal data associations between symptoms from the cross-lagged panel network analyses suggested that weaker associations in longitudinal analyses and a relatively weak autoregressive loop in the estimated network matrix clearly reduced the average number of activated symptoms.

Prior studies using both empirical and simulated data have suggested that network connectivity may be the key feature leading to “systemic” states with a large number of active symptoms, and thus, to prevalent depression (Cramer et al., 2016; van Borkulo et al., 2015a,b). Whereas some previous studies have supported this, negative findings have also been published (Airaksinen et al., 2020; Schweren et al., 2018). We did not find such a connectivity difference between the two groups. This was expected because a previous study using partly the same data also did not observe any differences in symptom connectivity between the groups (although that study used symptoms as continuous variables and modeled networks as GGMs). However, our results extend those of earlier studies by suggesting that the differences in symptom thresholds (the threshold for experiencing symptoms was lower in those with DD) may be the most important feature affecting symptom activation in the network. Symptom thresholds have traditionally been thought to be a result of higher connectivity or a result of a resilience factor (Kalish et al. preprint), but according to our findings threshold and connectivity are not mutually associated (or are associated negatively).

A novel feature of our study was also that we wanted to use the simulation to understand whether adding autoregressive feedback loops to the symptoms in the estimated network model would affect the number of potentially activated symptoms in the long run. This indeed seemed to be the case. Although the estimated follow-up time for the feedback loop may be unrealistic, our findings suggest that, as a group, those who do not get depressed may differ from those who end up with a lot of symptoms because of persistent autoregression effects (that Cremer and others (2016) call “critical slowing down”). People with depression (people with a higher number of symptoms) have a different ability to recover or again what could be called a lower “tipping point“ to move forth and back between having and not having specific symptoms (Cramer et al., 2016). According to our results, this does not seem to be associated with lower or higher connectivity, which is one of the take-home messages of this study.

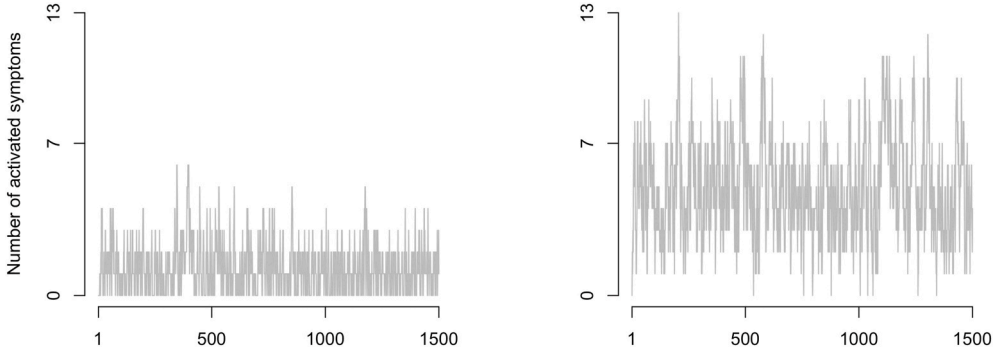

Fig. 3. Results of formal dynamic system model simulations of DD based on cross-sectional data. Left panels DD- and right panels DD+.

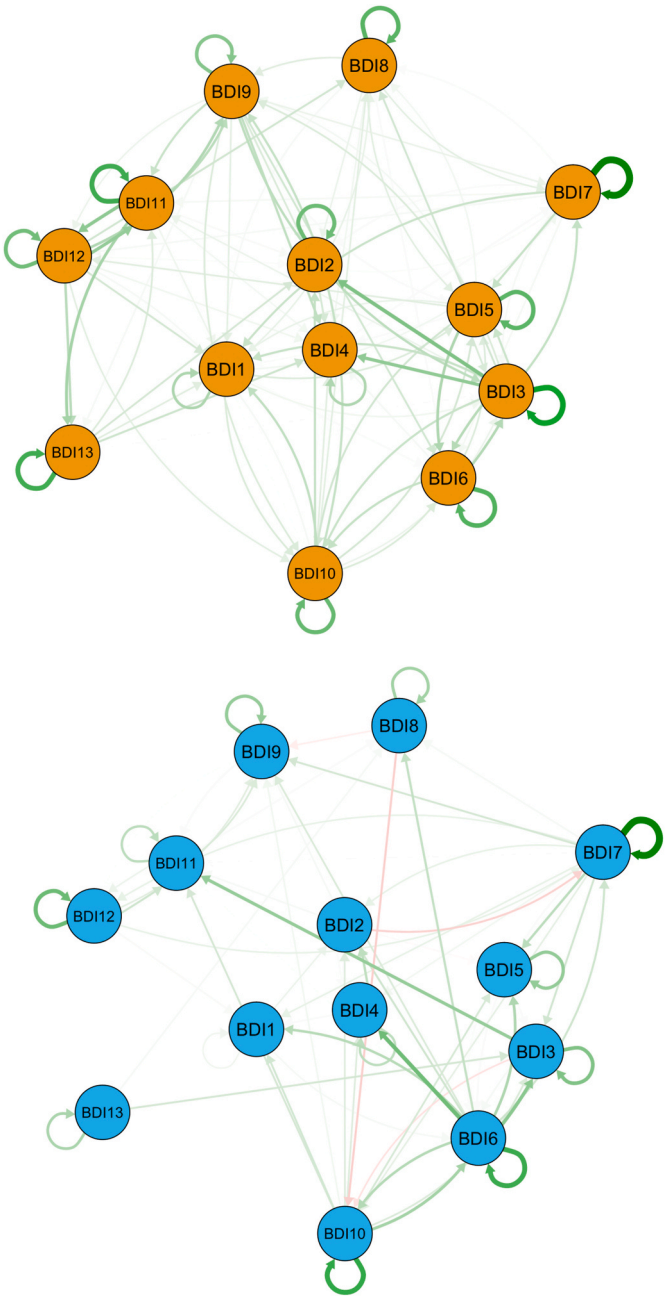

Fig. 4. Longitudinal cross-lagged panel networks in the DD-group (upper network) and the DD + group (lower network). The green circles represent autoregressive feedback loops, a bolded loop indicating a stronger autoregressive effect.
b1 = Depressed mood/sadness
b2 = Pessimistic about the future
b3 = Low self-esteem/past failure
b4 = Loss of pleasure/dissatisfaction
b5 = Feeling guilty
b6 = Feeling disappointed in oneself/self-dislike
b7 = Self-harm
b8 = Losing interest in other people
b9 = Difficulties in decision-making
b10 = Dissatisfaction with one's appearance/worthlessness
b11 = Work disability
b12 = Tiredness
b13 = Loss of appetite. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

5.1. Strengths and limitations

The main strengths of the study are the community sample, which is representative of the Finnish general adult population, and the use a structured interviews (CIDI) to identify participants with DD. Thus, we could compare DD+ and DD-groups without being forced to classify the groups based on the number of symptoms in the network. One of the problems when comparing the symptoms between two groups is the Berkson's bias. Berkson's bias may appear when a factor associated with a study's sampling framework gives rise to an aetiological association with the dependent variable of interest (Cole et al., 2010; de Ron et al., 2019). Berkson, who first pointed out this bias, identified the role of hospital sampling in the association between cholecystitis and diabetes. A hospital patient that does not have diabetes is more likely to have cholecystitis than a member of the general population, since the patient must have had some (possibly cholecystitis-causing) reason to enter the hospital in the first place that is not diabetes. This may result in a spurious negative association between the disease (cholecystitis) and the risk factor (diabetes). De Ron and others (2020) suggest that if one selects subsample based on the symptom reports and then analyze associations between the symptoms there may be spurious associations based on the Berkson's bias. Although we could not avoid the Berkson's bias, we did not have the most obvious sources bias, such as non-representative "control" group and subsamples based on symptom means.

A number of other limitations must be taken into account when interpreting the findings. The original sample of the Finnish Health 2011 survey included 4246 participants who were interviewed with the CIDI. The participants who did not participate in the CIDI interview have been shown to have had more depressive symptoms than those who participated (Pirkola et al., 2005a), indicating that they were more likely to suffer from DD. However, the aim of this study was not to estimate the prevalence of DD, and CIDI has been found to have acceptable psychometric properties (Wittchen, 1994). Among all possible depressive symptoms, we were limited to those included in BDI-13, and thus, other important symptoms may have been missed.

6. Conclusions

Our results replicated previous findings of very small differences in overall symptom connectivity of depressive symptoms between participants with and without DD. Our results also showed that the symptom threshold was lower in the DD + group than in the DD-group, and this predicted a higher number of activated symptoms in the future. The strength of the autoregressive feedback loops may be another important issue warranting consideration when testing the network theory of psychopathology and also in clinical practice when assessing recovery and relapse of individuals into and out of depressive symptoms. If replicated, these finding may have some crucial implications for the psychological network theory of psychopathology by underlining the importance of the symptom thresholds at least in addition to symptom connectivity in the development of psychiatric disorders. The importance of the symptom threshold may suggest that the psychological network theory of psychopathology needs to expand the networks by external factors affecting symptom thresholds, such as stressful life events, physiological risks (inflammation) and social relations.

Author statement

M.E. developed the study idea and designed the study. ME, JL and CH analysed the data. M.E. conducted the literature review and wrote the first draft of the manuscript. J.S. contributed to data acquisition. M. E., J.L., J.S., L.P-R. and C.H. contributed to the study conception or design or analysis or interpretation of the data. All authors contributed to critical revision of the manuscript for important intellectual content and approved the submitted manuscript.

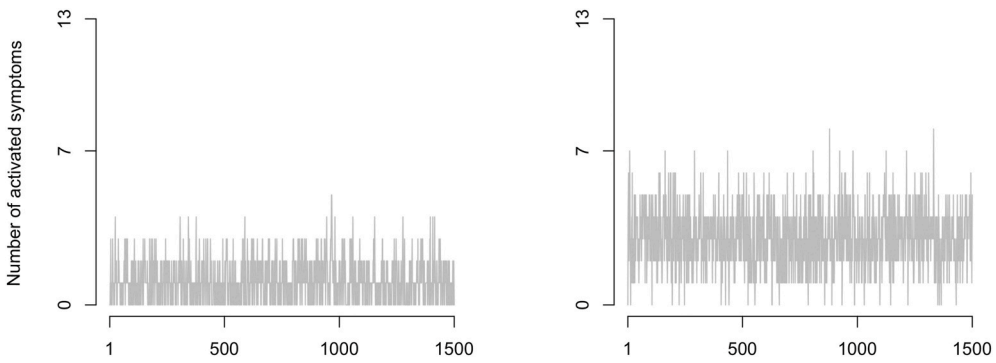

Fig. 5. Results of formal dynamic system model simulations of DD based on longitudinal data. Longitudinal data include autoregressive loops. Left panels DD- and right panels DD+.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.08.004.

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