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Research paper

Frequency and network analysis of depressive symptoms in patients with cancer compared to the general population

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ABSTRACT

Background: The use of sum scores of depressive symptoms has been increasingly criticized and may be particularly problematic in oncological settings. Frameworks analyzing individual symptoms and their interrelationships such as network analysis represent an emerging alternative.
Methods: We aimed to assess frequencies and interrelationships of 9 DSM-5 symptom criteria of major depression reported in the PHQ-9 questionnaire by 4020 patients with cancer and 4020 controls from the general population. We estimated unregularized Gaussian graphical models for both samples and compared network structures as well as predictability and centrality of individual symptoms.
Results: Depressive symptoms were more frequent, but less strongly intercorrelated in patients with cancer than in the general population. The overall network structure differed significantly between samples (correlation of adjacency matrices: rho = 0.73, largest between-group difference in any edge weight: 0.20, $p < 0.0001$). Post-hoc tests showed significant differences in interrelationships for four symptom pairs. The mean variance of symptoms explained by all other symptoms in the same network was lower among cancer patients than in the general population (29% vs. 43%).
Limitations: Cross-sectional data do not allow for temporal or causal inferences about the directions of associations and results from population-based samples may not apply to clinical psychiatric populations.
Conclusions: In patients with cancer, both somatic and cognitive/affective depression symptoms are less likely to be explained by other depressive symptoms than in the general population. Rather than assuming a consistent depression construct, future research should study individual depressive symptom patterns and their potential causes in patients with cancer.

1. Introduction

The level of depression, assessed by the sum score of a standardized self-report questionnaire, is among the most frequently reported psychological outcomes in the context of cancer care. Recent findings have however questioned the common practice to operationalize depression severity as the sum score of depressive symptoms. Two patients who have the same sum score on a depression questionnaire may not share a single symptom, due to the heterogeneity of symptom patterns (Fried and Nesse, 2015; Olbert et al., 2014). Using a single sum score of a depression measure further presumes that it is unidimensional, i.e. that all symptoms are roughly interchangeable measures of depression. A substantial body of psychometric research has, however, demonstrated that many common depression measures are multidimensional (Fried et al., 2016; Shafer, 2006). This means that, statistically, two or more scores better reflect how the measured depressive symptoms are intercorrelated with each other.

Using the sum score of depressive symptoms may be particularly problematic in oncological populations. The prevalence of depression in cancer tends to be much higher when assessed by sum scores and their cut-offs compared to standardized diagnostic interviews (Hartung et al., 2017a; Mehnert et al., 2014; Mitchell et al., 2011; Vehling et al., 2012). In addition, there is a large diagnostic discrepancy between the Patient Health Questionnaire-9 (PHQ-9), an established self-report depression questionnaire, and the standardized CIDI interview (Hartung et al., 2017b; Mehnert et al., 2014). Interestingly, this discrepancy was larger in cancer patients than in general medical patients across all possible cutoff values of the PHQ-9 (Hartung et al., 2017b; Löwe et al., 2004b). While algorithms which prioritize some items over others may achieve better accuracy than sum scores weighting all items equally (Lie et al.,

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2015), there is evidence that even the best-established algorithms show a low diagnostic accuracy compared to a standardized interview in oncological settings (Hartung et al., 2017b). In addition, there is evidence for multidimensionality of frequently used depression questionnaires such as the Hospital Anxiety and Depression Scale (HADS) in oncological samples, suggesting that the one-factor solution may be at least as problematic in patients with cancer as in other patient populations (Hinz et al., 2016).

These recent findings contribute to a long-lasting debate about the adequacy of standard diagnostic criteria of depression in patients with cancer. Several approaches to exclude or replace depression criteria confounded by medical illness such as fatigue, diminished appetite, sleep disturbance, and diminished concentration have been proposed (Trask, 2004; Zimmerman et al., 2006). Although evidence on this issue is limited, studies suggest that patients with cancer report all depressive symptoms significantly more often than the general population, with particularly large differences in somatic symptoms (Hinz et al., 2016, 2010; Osborne et al., 2004). Consequently, excluding or substituting somatic symptoms leads to substantially different prevalence estimates of depression (Saracino et al., 2018; Sharpley et al., 2017). Yet, few studies have investigated the interrelationship between somatic and cognitive-emotional depressive symptoms in cancer (Jones et al., 2015; Mitchell et al., 2012, Nikendei et al., 2018). These studies consistently found no relevant differences in item functioning or diagnostic utility between somatic and non-somatic depression symptoms. However, none of the studies used a representative control group (either no non-cancer control group at all or only psychiatric control patients with an even higher depression severity than in the depressed patients with cancer).

Thus, it is still unclear (1) to what extent patients with cancer differ from the general population in terms of individual depressive symptoms, (2) how depressive symptoms are interrelated with each other among patients with cancer, and (3) whether these interrelationships among individual depressive symptoms differ from those in the general population, which may be relevant to the diagnosis and treatment of depression in patients with cancer.

One approach to address these questions is the symptomics framework (Fried, 2017), which focuses on individual symptoms and their (potentially causal) relationships among each other. Conceptually, this framework understands individual depression symptoms as important constructs in their own right (Persons, 1986) — concentration problems are viewed as a different entity than suicidal ideation or sadness, rather than as expressions of the same underlying process — and conceptualizes depression as an emergent property that may arise due to associations and vicious circles among symptoms. This theoretical framework can be statistically investigated via network psychometrics (Epskamp, 2017). Estimated network models can be visualized: they contain nodes (symptoms) and edges (relationships among pairs of nodes), usually computed as partial correlations (Borsboom, 2017). To our knowledge, this approach has not been applied to depressive symptoms in patients with cancer so far.

Therefore, the aim of this study was to assess and compare frequency and severity of individual depressive symptoms in patients with cancer and the general population and to explore the interrelations among these symptoms using network models. We estimated and compared the overall network structure, predictability and centrality of depressive symptoms across samples from two populations: patients with cancer and the general population.

2. Methods

2.1. Participants and data collection

We analyzed data from two studies: The first is a representative sample of 4020 patients with cancer with all major cancer types, recruited in a cross-sectional, prospective, multicenter study in five regions across Germany between 2007 and 2011 (Hartung et al., 2017a; Mehnert et al., 2014, 2012). Patients were recruited from a total of 84 inpatient wards, outpatient clinics and cancer rehabilitation centers during cancer treatment or follow-up, stratified by cancer type in proportion to the nation-wide cancer incidence. Patients were asked to fill in the questionnaires at their respective cancer treatment or rehabilitation center.

The second sample was selected from two nationally representative general population surveys conducted in Germany between 2003 and 2008 (n = 2500 and n = 2518) (Kocalevent et al., 2013). Here, randomly selected participants were given questionnaires during home visits. From the total sample (n = 5018), 4020 controls were automatically matched to patients first by sex and second by age (as closely as possible) using the *matchControls* function from the R package *e1071* (Meyer et al., 2017).

2.2. Measures

Sociodemographic data were collected with standardized questionnaires and medical data were collected from hospital charts.

Depressive symptoms were assessed with the German version of the Patient Health Questionnaire 9-item Depression Module (PHQ-9), which is a validated, reliable and widely used self-report measure with an internal reliability of Cronbach's $\alpha = 0.89$ and a test-retest correlation $r = 0.84$ within 48 h in primary care patients (Kroenke et al., 2001; Löwe et al., 2004a). Participants are asked to report the occurrence of each of the 9 depressive symptom criteria in the DSM-IV during the past two weeks as '0' (not at all), '1' (several days), '2' (more than half the days), or '3' (nearly every day): (1) interest loss ("Little interest or pleasure in doing things"), (2) depressed mood ("Feeling down, depressed or hopeless"), (3) sleep ("Trouble falling asleep, staying asleep, or sleeping too much"), (4) energy loss ("Feeling tired or having little energy"), (5) appetite change ("Poor appetite or overeating"), (6) worthlessness ("Feeling bad about yourself – or that you're a failure or have let yourself or your family down"), (7) trouble concentrating ("Trouble concentrating on things, such as reading the newspaper or watching television"), (8) psychomotor issues ("Moving or speaking so slowly that other people could have noticed. Or, the opposite – being so fidgety or restless that you have been moving around a lot more than usual"), (9) suicidality ("Thoughts that you would be better off dead or of hurting yourself in some way").

2.3. Statistical procedures

All statistical analyses were performed using R Version 3.3.1. All tests were two-sided and p-values of multiple comparisons were Holm–Bonferroni corrected.

To estimate the frequency (and 95% confidence interval) of each symptom, symptom scores were dichotomized at the cutoff ≥ 2 (occurring more than half the days during the past two weeks). Means were compared using t-tests, frequencies using chi-squared tests.

Network structures of PHQ-9 items in each group were analyzed as follows. Spearman's correlation matrices for each group were calculated. Based on these correlations, interrelationships between items were estimated as partial correlations. As our dataset contained only nine variables but thousands of observations, regularization was not needed (Williams and Rast, 2018). Therefore, unregularized Gaussian graphical models (GGM) were computed using the *ggmModSelect* function from the package *qgraph* (version 1.5)(Epskamp et al., 2012). The function runs the graphical least absolute shrinkage and selection operator (glasso) for 100 different tuning parameters to obtain 100 different network structures. It then chooses the best model according to the Bayesian information criterion (BIC) and then tests all possible ways to improve the BIC by adding or removing edges.

The predictability of each node was estimated using the package *mgm* (Haslbeck and Fried, 2017). Predictability is defined as the

Table 1
Descriptive item statistics and group differences.

		General population				Patients with cancer				Hedges' *g*
		M	SD	Pred	Strength[a]	M	SD	Pred	Strength[a]	
1	Interest loss	0.48	0.62	41%	−0.72	0.85	0.89	33%	0.36	0.48***
2	Depressed mood	0.34	0.59	52%	1.83	0.67	0.75	39%	1.41	0.49***
3	Sleep	0.56	0.72	40%	−0.67	1.35	1.08	25%	−0.66	0.86***
4	Energy loss	0.60	0.69	50%	1.11	1.21	0.96	42%	1.74	0.73***
5	Appetite change	0.26	0.55	38%	−0.44	0.80	1.01	27%	−0.56	0.66***
6	Worthlessness	0.19	0.48	45%	0.48	0.27	0.60	24%	−0.58	0.14***
7	Trouble concentrating	0.34	0.58	42%	−0.14	0.70	0.84	29%	0.07	0.50***
8	Psychomotor issues	0.14	0.43	40%	−0.02	0.43	0.77	21%	−0.60	0.47***
9	Suicidality	0.09	0.34	39%	−1.42	0.17	0.44	22%	−1.17	0.20***

Abbreviations: M, mean; SD, standard deviation; Pred, predictability (proportion of the variance explained by all other symptoms in the network).
[a] Standardized node strength centrality (sum of edge weights connected with the node).
*** $p < 0.001$ after Holm–Bonferroni correction.

variance in a node that is explained by all other nodes in the network. The resulting network was analyzed using node strength centrality, an index from graph theory (Epskamp et al., 2018; Opsahl et al., 2010). The strength of a node is equal to the sum of all absolute associations, e.g. partial correlations that this node exhibits with all other nodes.

The network models were graphed using the Fruchterman–Reingold algorithm ("spring" layout from package *qgraph*), representing items as nodes and partial correlation coefficients as lines between the nodes, referred to as "edges". In this layout, highly correlated nodes are placed closer together, such that nodes with many strong correlations appear near the center of the network and nodes with fewer and/or weaker correlations are pushed to the periphery. To facilitate visual comparison of the networks, the average layout across both samples is presented. Predictability was visualized as a ring-shaped pie chart around the nodes, i.e. a completely filled ring would indicate that 100% of the variance of the node is explained by its correlations with the other symptoms of the network.

The structural similarity of the two networks was estimated using the Spearman correlation of the two adjacency matrices, i.e. the matrices of edge weights for each network (Fried et al., 2018; Rhemtulla et al., 2016). To estimate differences in the relationships between depressive symptoms in the two populations, we statistically compared differences in network structures with the Network Comparison Test (NCT) (van Borkulo et al., 2016). The NCT is a permutation test which randomly splits the data set and refits the network models repeatedly (1000 times in our analysis) to generate a reference distribution representing the null-hypothesis that there is no difference between the networks estimated in the two observed groups (in our case, general population vs. patients with cancer). The significance of group differences in three parameters can be tested in relation to the reference distribution: (1) network structure, quantified as the maximum difference in any edge weight, (2) differences in individual edge weights, and (3) difference of global network strength, defined as the sum of all node strengths. To achieve results exactly matching the network models above, the NCT was performed with a modified version of the package *NetworkComparisonTest* (Jones, 2018) which allowed for unregularized networks of Spearman correlations.

2.4. Sensitivity analyses

Unregularized model search for GGM is a relatively new approach especially suited for data like ours with few variables and many observations. As this is less established than regularized model search algorithms, we evaluated potential differences between the adjacency matrices (i.e., the edge weights) resulting from unregularized and regularized network models by Spearman correlations. We further compared the adjacency matrices resulting from unregularized and neighborhood regression network models (which were the basis for predictability estimates). As suggested by one of the reviewers, we performed subgroup analyses for patients in curative and palliative cancer treatment.

2.5. Ethics and transparency

The original studies were conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008. All participants provided written informed consent and data protection was secured in accordance with German data protection laws (§§27-30a BDSG; Kocalevent et al., 2013; Mehnert et al., 2012). The patients study was approved by ethics committees in all federal states involved (Mehnert et al., 2012). R-code and correlation matrices are provided as Supplementary materials online (www.osf.io/px9gk).

3. Results

3.1. Participants

Detailed sample characteristics were published previously for both the general population sample (Kocalevent et al., 2013) and patients with cancer (Hartung et al., 2017a) but are briefly summarized as follows: There were 51% women in both samples. Mean age was 55 years (SD = 15 years) in the general population sample and 58 years (SD = 11 years) in patients with cancer. In patients with cancer, the mean time since diagnosis was 14 months (SD = 25 months). The most frequent tumor locations were breast ($n = 906$), prostate ($n = 637$), colorectal ($n = 510$), female genital organs ($n = 317$) and hematological ($n = 305$).

3.2. Item scores and correlations

All PHQ-9 items showed significantly higher mean values in patients with cancer than in the general population (Table 1). Item standard deviations were larger in patients with cancer and distribution of values was more skewed towards lower values in the general population (Table 1 and Supplementary material S1). When dichotomizing PHQ-9 items, all depressive symptoms ($p < 0.001$) except suicidality ($p > 0.243$) were significantly more common in patients with cancer than in the general population (Fig. 1). In both groups, the two most common symptoms were sleep and energy loss, while suicidality was the least common symptom.

All symptoms showed significant correlations with all other symptoms with medium Spearman correlations in the general population (median $r = 0.41$) and somewhat smaller correlations in patients with cancer (median $r = 0.31$; Supplementary material S2).

3.3. Network models

Partial correlation networks for both groups are shown in Fig. 2. In

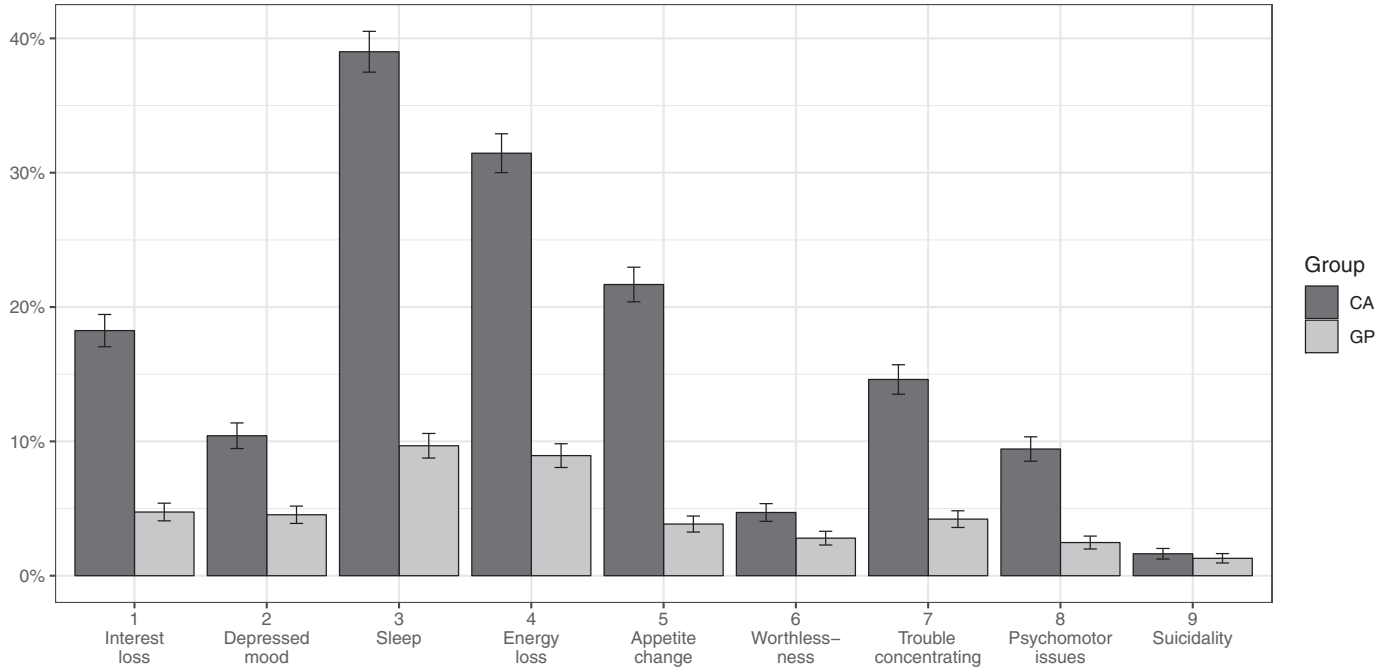

Fig. 1. Relative frequency and 95% confidence intervals of PHQ-9 depressive symptoms in patients with cancer (CA) and controls from the general population (GP). Symptom scores were dichotomized at the cutoff ≥2 (occurring more than half the days during the past two weeks).

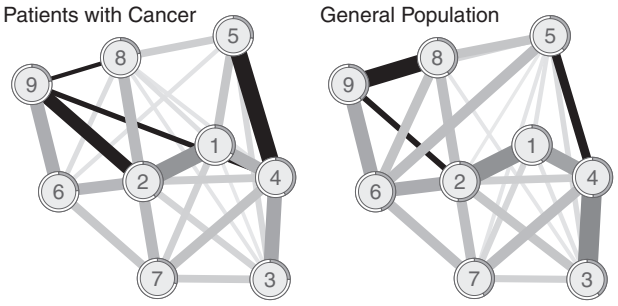

Fig. 2. Partial correlation networks of PHQ-9 depressive symptoms in patients with cancer and controls from the general population. Ring-shaped pie charts represent predictability (a fully filled dark ring would indicate that 100% of the symptom's variance is explained by its intercorrelations with the other symptoms in the network), edges that differ significantly in size across networks are shown in black (see Supplement Table S3 for edge weights and their difference). Legend: 1 Interest loss, 2 Depressed mood, 3 Sleep, 4 Energy loss, 5 Appetite change, 6 Worthlessness, 7 Trouble concentrating, 8 Psychomotor issues, 9 Suicidality.

both groups, 27 out of all possible 36 edges (75%) had an absolute weight above zero. In the general population, the strongest edges were sleep—energy loss, interest loss—depressed mood, psychomotor issues—suicidality; in patients with cancer, the strongest edges were interest loss—depressed mood, energy loss—appetite change and sleep—energy loss (Supplementary material S3). The predictability of symptoms, i.e. the percentage of a node's variance explained by all other symptoms in the network, is shown as ring-shaped pie charts in Fig. 2. Mean predictability was 43% in the general population and 29% in patients with cancer. Depressed mood (52%), energy loss (50%) and worthlessness (45%) had the highest predictability in the general population, while energy loss (42%), depressed mood (40%), and interest loss (33%) had the highest predictability in patients with cancer.

Standardized node strength centrality differed substantially for interest loss and worthlessness (Fig. 3).

3.4. Comparison of networks

While considerable similarities between adjacency matrices (Spearman's rho = 0.73) and node strength centralities (rho = 0.79) emerged, the NCT revealed significant differences between the two networks on a structural level: the maximum difference in any edge weight was 0.20 ($p < 0.0001$), indicating significantly different overall structure. Post-hoc tests showed that four out of 36 edges (11%) had significantly different weights in the two networks (all $p < 0.0001$): energy loss—appetite change, depressed mood—suicidality, energy loss—suicidality and psychomotor issues—suicidality (Fig. 2). In addition, global strength differed significantly between the two networks (general population: 3.80, patients with cancer: 3.47, $p < 0.0001$), which means that the general population network was more densely connected. This is in alignment with the larger average predictability values in the general population network.

3.5. Sensitivity analyses

Overall, our particular modeling choice (unregularized GGM model selection using Spearman correlations) did not have an impact on the obtained results; results were essentially unchanged using neighborhood regression (all absolute differences in edge weights ≤ 0.05; Spearman correlation of adjacency matrices rho: 0.95 and 0.97; Supplementary Material S4) and regularized approach (all absolute differences in edge weights ≤ 0.04; Spearman correlation of adjacency matrices rho: 0.99 and 0.98; Supplementary Material S5). This speaks to the robustness of both our results and the different network estimation routines. Subgroup analyses showed that all symptoms except worthlessness and trouble concentrating were significantly more severe in patients in palliative compared to curative cancer treatment while there were no substantial differences in interrelationships and network structures (Supplementary materials available at www.osf.io/px9gk).

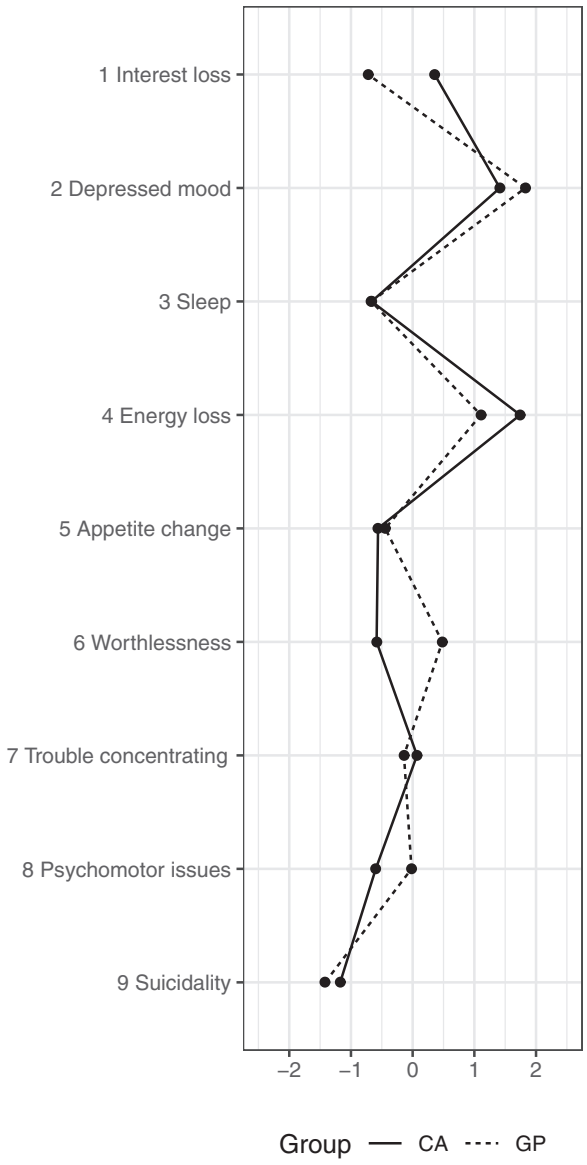

Fig. 3. Standardized node strength centrality for PHQ-9 depressive symptoms in patients with cancer (CA) and the general population (GP).

4. Discussion

4.1. General results

This is the first study to compare network structures of depressive symptoms in patients with cancer and the general population. Depressive symptoms showed a significantly lower global connectivity in patients with cancer compared to the general population. This suggests that symptoms tend to depend less on other symptoms in the network in cancer patients. Consistent with this finding, all symptoms showed lower predictability (proportion of variance explained by all other symptoms in the network) in individuals with cancer than in the general population. One interpretation of this finding is that, in cancer populations, a larger proportion of the variance of depressive symptoms is explained by external variables which do not appear in the network. Such variables may include tumor- and treatment-related factors such as pain, neurological deficits, chemotherapy or hormone therapy (Jones et al., 2015).

4.2. Frequency of depressive symptoms

All depressive symptoms were reported more frequently in patients with cancer than in the general population sample, which is consistent with previous studies (Hinz et al., 2016, 2010; Osborne et al., 2004). This difference was particularly large for somatic symptoms such as sleep problems, energy loss and appetite change, which may directly or indirectly be caused by cancer and its treatment.

4.3. Symptom-level group differences

Four items showed substantial differences between the two groups: sleep, worthlessness, interest loss, and suicidal ideation. Sleep disturbances were significantly more common in patients with cancer than in the general population, showing the largest standardized difference in mean scores between groups (Hedges' $g = 0.86$). While this symptom also had a substantially lower predictability in patients with cancer (25% vs. 40% in the general population), there was no difference in relative node strength centrality and none of the edges connected to this node differed significantly between groups. This suggests that sleep disturbances may be substantially more frequent due to factors other than depressive symptoms, while still bearing a similar relationship to other depressive symptoms and/or their causes as in the general population.

Worthlessness ("feeling bad about oneself") showed the largest difference in predictability between groups (45% in the general population vs. 24% in patients with cancer). This symptom was much less predictable and, at the same time, much less central among cancer patients. One possible explanation for this interesting structural difference between the networks with regard to a sense of worthlessness may lie in the psychological underpinnings of cancer-related stressors. Depression theories discuss that a bias to blame oneself for failure in an overgeneralized way may underlie this symptom pathophysiologically (Zahn et al., 2015). These mechanisms may however be much less relevant for individuals with cancer, who are frequently confronted with dignity- and self-worth-threatening situations (changes in appearance, loss of functioning, dependency). Thus, we speculate that in some cases a sense of worthlessness may be more strongly associated with such external cancer-related factors than with negative cognitive biases in patients with cancer.

Centrality measures such as node strength centrality may guide the search for symptoms that activate or maintain psychopathology networks. Energy loss was the most central symptom in patients with cancer (standardized node strength centrality 1.74). Longitudinal studies are needed to assess whether this symptom precedes associated symptoms or whether it represents their common end points. If the former is the case, patients' energy levels may improve a whole range of depressive symptoms. Anhedonia or loss of interest was substantially more central in patients with cancer than in the general population, showing the largest positive group difference in relative node strength (standardized node strength centrality 0.36 vs. −0.72 respectively). Future research could assess whether special attention to this symptom may improve diagnostics and therapy in oncological populations.

Suicidal ideation had the largest number of significantly different edges between groups, while it was similarly central in both networks. This suggests that this symptom plays a similar role in the overall network, while being associated with different symptoms within the network. Among patients with cancer, suicidal ideation, especially in the more passive form of thoughts about death, can have different meanings. On the one hand, it could be part of a state of severe despair, which would explain the strong link to lowered mood in the network (Nissim et al., 2009); but it could, among patients with terminal cancer, also indicate a feeling of acceptance and letting go, which may explain the residual association with loss of energy in cancer, which did not emerge in the general population. For another subgroup of patients, endorsing the suicidality item on the PHQ-9 could reflect a process of

self-confronting coping with their life-threatening disease. The differential relationships in the cancer network thus underline the complexity of this symptom in cancer.

The role of suicidality within the network of depressive symptoms may also differ between patients with early and those with advanced disease. When facing a life-threatening disease, suicidality may decrease as the threat of one's life is already located in the (exterior) disease and thus diminishes the (internal) desire to end one's life.[1] However, our subgroup analyses showed that suicidal thoughts were significantly more severe in patients in palliative treatment compared to patients in curative treatment and we found no substantial differences in network structures between the two groups.

4.4. Implications for diagnostics and treatment in oncological settings

The low cohesion and within-network predictability of depressive symptoms in patients with cancer are consistent with the idea that many depressive symptoms may be caused by factors outside the symptom network. Some of these factors may be related to cancer and its treatment. Such causal hypotheses can be formulated not only for somatic symptoms, but also for cognitive and affective symptoms, as discussed above. While somatic symptoms of depression may be particularly common in patients with cancer, these symptoms did not stand out in terms of their interrelationships with other depression symptoms. Our results underline the heterogeneity of depressive symptom patterns and the complex roles that individual symptoms may play in patients' overall psychosocial symptom burden.

Although depression symptoms are very frequent in cancer, health care professionals often feel badly equipped to manage them (Kissane, 2014). In this regard, our results tie in with an increasing acknowledgement in the literature that the concept of depression as a psychiatric category may be of limited use for clinical management of depression symptoms in the cancer context (King, 2017). Our results add further insights into this observed mismatch. While a sum score of depressive symptoms can serve as an indicator of psychosocial symptom burden, clinicians should assess symptoms individually and consider potential causes and solutions for each symptom in a patient-centered approach. This may occur in a psychotherapeutic context, but can also guide oncological treatment decisions and side-effect management, as well as inform pharmacological treatment choices.

4.5. Strengths and limitations

Strengths of our study include the large, representative population-based samples; highly accurately estimated parameters in the network models; and sensitivity analyses demonstrating that the particular choice of network model did not affect the results.

Our results ought to be interpreted in light of the following limitations: First, the data we analyzed stemmed from cross-sectional studies, which do not allow temporal or causal inferences about the directions of the observed associations. Second, we analyzed population-based samples, in which most of the participants did not fulfill the criteria of a mental disorder; results can thus not be generalized to clinical psychiatric populations. Third, while the PHQ-9 is a psychometrically strong instrument adhering to the DSM-5 criteria of major depression, it does not deliver the same level of detail as longer questionnaires and partially achieves its brevity by combining two directions of a symptom in a single bidirectional item (e.g. appetite loss or gain). Future studies could obtain more fine-grained results by using longer scales which distinguish between all possible directions of symptoms.

[1] We would like to thank an anonymous reviewer for suggesting this important interpretation.

4.6. Conclusion

Although depressive symptoms are much more frequent in individuals with cancer, they are less cohesively related to each other. Depression symptoms are more likely to be associated with non-symptom factors in patients with cancer than in the general population. Notably, the present results indicate that this pattern does not only apply to somatic, but also to cognitive and affective depressive symptoms. The significant structural differences between the networks further strengthen the need to better understand what lies behind depressive symptoms in cancer. A more detailed inquiry into the pathways from disease and treatment-related factors to such symptoms can inform psychosocial interventions to aim beyond “alleviating depression”. Rather than assuming a consistent depression construct, individual depressive symptom patterns and their potential causes should be considered in individuals with cancer.

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CRediT authorship contribution statement

Tim J. Hartung: Methodology, Formal analysis, Investigation, Writing - original draft, Visualization. **Eiko I. Fried:** Formal analysis, Investigation, Visualization, Supervision. **Anja Mehnert:** Resources, Data curation, Visualization, Funding acquisition. **Andreas Hinz:** Resources, Data curation, Writing - original draft, Visualization, Funding acquisition. **Sigrun Vehling:** Methodology, Formal analysis, Visualization, Project administration.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.06.009.

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