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The Complex Interplay of Pain, Depression, and Anxiety Symptoms in Patients with Chronic Pain: A Network Approach

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ABSTRACT

Objectives: This study aimed to analyze the associations among depressive/anxiety and pain symptoms in patients diagnosed with chronic pain. **Methods:** Four hundred and fifty-four inpatients who were consecutively admitted in a multimodal 3-weeks treatment in a tertiary psychosomatic university clinic completed 25 items from the *Brief Pain Inventory* and the *Hospital Anxiety and Depression Scale* at baseline and after treatment termination. Associations among symptoms were explored by network analyses using the graphical least absolute shrinkage and selection operator to estimate their partial correlations, while Extended Bayesian Information Criterion was used to select the best network solution for the data. We explored symptoms' centrality and expected influence within the network as well as the minimum spanning tree for the network. **Results:** Besides expected associations within depressive/anxiety and pain symptoms, the estimated network showed several local associations between depressive and pain interference symptoms. The lacks of being cheerful and of laughing are two of the depressive symptoms that showed the greatest associations with pain interference and a strong centrality within the network. Sleep problems were both associated with anxiety/depressive symptoms and pain intensity symptoms. Although at post-treatment, most of the symptoms showed a significant decrease, the strength of the associations between the symptoms within the network were significantly higher than at baseline. **Discussion:** The results support focusing psychosocial interventions in chronic pain treatment not only on reducing pain, anxiety and sleep symptoms but also on enhancing positive affect. Future research is needed to replicate these findings using repeated within-person measures designs.

Conflicts of interests: the authors declare no conflict of interest.

Key words: Network Analysis; Chronic Pain; Anxiety; Depression

INTRODUCTION

Relationship between depression, anxiety and chronic pain

Empirical research has shown strong associations among chronic pain (CP) and depressive and anxiety symptoms. The percentage of patients with depression is double in people with CP (30% vs. 15%) compared to no CP controls, and the prevalence of anxiety disorders in CP patients is 50% higher than in controls (21% vs. 14%).[1] In addition, there is a significant correlation between lifetime prevalence of depression and pain incidents.[2] Pain intensity, number of pain locations, and the amount of days with pain are significantly associated both with depression and anxiety severity[3] as well as with the likelihood of being diagnosed with depression.[4] In addition, being diagnosed with a mood or anxiety disorder is related to an increase in the likelihood of having pain syndromes concurrently.[2,5] Furthermore, a diagnosis of a CP disorder increases the risk of being diagnosed with an anxiety or depressive disorder in the future.[6,7] Conversely, a previous diagnosis of depression or an anxiety disorders is significantly associated with a future diagnosis of chronic pain.[8]

Symptoms network analysis

While the link among mood and anxiety disorders and chronic pain has been well established in previous research, we lack empirical research to sufficiently understand the specific associations between *symptoms* of chronic pain, anxiety, and depression. *Network analysis* (NA) is a methodology that might enhance our understanding, providing a more fine-grained analysis at the symptom level that may have direct clinical implications, such as the identification of the most important symptom in a network that should be given priority in the treatment of chronic pain.

Recent research in depression has emphasized the potential importance of a symptom-level instead of a syndrome-level perspective.[9] For example, individual symptomatology analysis have improved the accuracy of mainstream summary strategies based on a broader amount of symptoms (e.g., analysis of overall severity) to predict the onset of a depression.[10]

For other diagnostic groups, network analyses at the symptom level has already helped to better understand psychopathological comorbidity patterns (e.g. depression and anxiety,[11] social anxiety and eating disorders,[12] eating disorders, depression, and anxiety,[13] generalized anxiety and depression[14]).

The network approach in clinical psychology is founded on an innovative psychopathological perspective.[15,16] Historically, mental disorders have been considered as latent (i.e. unobservable) entities that *cause* an observable constellation of symptoms. For example, if someone experiences a combination of depressed mood, anhedonia, apathy, abulia, self-reproach tendencies, insomnia, fatigue, and concentration problems this might be because the person suffers from a major depressive disorder.[16,17] This psychopathological conceptualization implies, based on the classical medical model of disease causation, that the association between the observed symptoms can be *explained* by the existence of an underlying, latent mental disorder.[16] As a consequence, symptoms need to be independent from each other and their association (i.e. its joint occurrence) should disappear if the effect of the latent condition is controlled for.[17] However, the independence of symptoms cannot be supported by psychopathology research.[17,18] For example, in case of a depressed person, it is very likely that the experience of a depressed mood may also increase self-reproach behaviors, while rumination may contribute to problems in sleeping, which in turn may increase the person's fatigue-level, which may lead to concentration problems.[19]

To overcome these shortcomings, several authors recently proposed an alternative model for explaining the co-occurrence of certain symptoms within and across disorders (i.e. comorbidity). In these models, symptoms are conceptualized as being *interdependent* and jointly forming a psychopathological mental condition instead of assuming an underlying latent disease or disorder that explains the presence of a number of *independent* symptoms.[15,19,20] Thus, the network of associations among the symptoms constitutes the syndromes and not the other way around.[15] From a clinical point of view, this perspective

might have fundamental implications. It means that changes in one symptom might produce changes in the other symptoms (and in the whole network), and interventions may try to produce changes in the whole network structure by focusing on specific central symptoms.[15,21]

To analyze systematic associations among symptoms, NA provides a visual and statistical tool that paves the way for gathering evidence of the importance of each single symptom in the complex network of symptoms.[22] We are going to provide a more detailed explanation of NA in the methods section.

Network analysis of depressive and anxiety symptoms in chronic pain patients

In our literature search, we found only few and very recent examples of studies analyzing depressive and anxiety symptoms in patients with chronic pain using network analysis. McWilliams, Sarty, Kowal, and Wilson[23] used this method to study the association among depressive symptoms in patients with chronic pain. In this study, the most central symptoms (in terms of their connectivity within the network[24]) were depressive mood, difficulty concentrating, loss of interest, and fatigue. Depressive mood was the symptom with the highest strength (i.e., a measure of centrality based on how strong the connections with the other symptoms are). Difficulty concentrating was the symptom with the highest closeness (i.e., measure of centrality based on distance between the symptoms) and betweenness (i.e., measure of centrality based on how important a symptom is to connect others). After depressive mood and difficulty concentrating, loss of interest and fatigue symptoms were the symptoms with the higher centrality strength, closeness, and betweenness within the network.

More recently, Thompson, Broadbent, Fuller-Tyszkiewicz, Bertino, and Staiger[25] used complex network analysis to explore the association of anxiety and depression severity with pain severity indices (i.e. pain intensity and pain interference with daily life), and fear avoidance. Results showed that overall depression severity seemed to play a fundamental role within the network, being the construct with the highest strength, and that the associations of anxiety within the whole network were mediated by depression symptoms. Furthermore,

perceived pain interference was the construct with the greatest closeness and betweenness followed by fear avoidance.

While the studies by McWilliams et al.[23] and Thompson et al.[25] made meaningful contributions to our understanding of the complex associations among depressive, anxiety, and pain symptoms, the current study builds upon this evidence and tries to further our knowledge in several ways. First, McWilliams et al.[23] conducted fine-grained analyses of depressive symptoms in chronic pain patients, but did neither include the core pain symptomatology nor anxiety symptoms in their analyses. Second, Thompson et al.[25] incorporated both mood and anxiety symptoms as well as pain severity indices, but used scale-level information, without exploring the specific associations between single mood, anxiety, and pain symptoms. Consequently, while this study supported the idea of interrelations among these constructs, focusing on specific associations between single symptoms and their relevance might increase our understanding of the complex interplay among depression, anxiety, and pain symptoms.

Thus, the aim of the current study is to analyze the network structure of the associations among depressive symptoms, anxiety symptoms, and pain severity indices in chronic pain patients. We will first focus on analyzing patients' baseline network of associations among these symptoms (aim #1). Then, we will analyze the symptoms network at post-treatment, comparing it with the one identified at baseline (aim #2). Finally, we will compare the network structures of responders and non-responders to treatment (aim #3). To define responders we followed the suggestions by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT[26]). In their consensus statement for chronic pain patients, the IMMPACT recommended considering a change as clinically relevant if the patient presents a reduction in the sub-scale *pain interference with daily life* of the Brief Pain Inventory (BPI) that is equal to or greater than half a standard deviation of the sub-scale.[26]

The results of this study might help to enhance treatments for chronic pain by identifying relevant anxiety and depression symptoms that might be targeted by focused interventions within a multi-modal treatment.

MATERIALS AND METHODS

Participants

Four hundred fifty-four inpatients being diagnosed with chronic pain disorder with somatic and psychological factors (F45.41[27]) who were consecutively admitted into an interdisciplinary multimodal treatment program at a tertiary psychosomatic university clinic in Switzerland were included in the sample.

On average, participants were 45.50 years old (SD= 15.04), mostly women (60.9%), married (42.6%) or in a relationship (12.7%), and had at least a high school degree (79.2%). Most of the participants either were Swiss by birth (58.7%) or naturalized Swiss (27.4%). The majority of the sample suffered from pain symptoms for more than a year (84.6%), and more than one quarter of the participants for more than 10 years (26.1%). 60.4% of them was unable to work.

Treatment

Inpatient treatment consisted of a three-week program that comprised different multifaceted interventions and therapies. Besides medical interventions and pharmacotherapy, the program entailed individual and group physiotherapy. As well patients were enrolled in ergotherapy, individual psychotherapy (that consists of cognitive behavioral therapy and biofeedback), group psychotherapy (focused on pain management, vertigo/dizziness management, communication group), and relaxation training (i.e., mindfulness).

Measures

Depression and anxiety symptoms. To assess depression and anxiety symptomatology, we used the German version of the Hospital Anxiety and Depression Scale (HADS[28]), a measure designed to detect manifestations of anxiety and depression in patients

with physical illnesses or somatoform complaints. The HADS is a self-report instrument, rated on a Likert scale from 0 (*not at all*) to 3 (*most of the time*). As this measure excludes anxiety and depression items that are strongly associated with physical symptoms, it is recommended for chronic pain populations [29]. The HADS assesses the degree of depressive and anxiety symptoms during the past week with two subscales (i.e. anxiety and depression) that have seven items each. As in this study for the descriptive analyses we used the mean subscale score (i.e., total score / number of items responded), the theoretical range of each subscale was from 0 to 3. The anxiety subscale includes items such "I feel tense or 'wound up'", while the depression subscale includes items as "I feel as if I am slowed down". Some items included in the HADS represent positive emotions or states (being cheerful, being able to laugh, being able to enjoy things, feel relaxed, etc.). In those cases, items were reverse scored, assuming that the lack of those positive features represent either depressive or anxiety symptoms. The HADS showed adequate psychometric properties with good internal consistency, sensitivity and specificity, external validity, and construct validity (showing a two-factors structure).[30] In the current sample, the HADS subscales showed adequate internal consistency with Cronbach's alphas of .77 and .82 for anxiety and depression subscales at baseline, respectively.

Pain symptoms. For pain assessment, we used the German version of the Brief Pain Inventory (BPI).[31] Originally designed to assess cancer pain, the BPI is now frequently used as a generic pain questionnaire for various chronic pain conditions.[32] This self-report measure has two subscales to evaluate patient's pain: pain intensity and pain-related interference in the patient's life. The pain intensity subscale has four items measuring the severity of the pain experience that are rated on an 11-point numeric rating scale from 0 (*no pain*) to 10 (*most imaginable pain*). For example, one item of the pain intensity subscale is "rate your pain by marking the number that best describes your pain at its worst in the last 24 hours". The pain interference subscale has seven items rated also on an 11-point numeric rating scale from 0

(*does not interfere*) to 10 (*completely interferes*). This subscale includes items such as "mark the number that describes how, during the past 24 hours, pain has interfered with your general activity". In terms of timeframe, three items of the pain intensity subscale refers to the last 24 hours (i.e., worst pain, least pain, and average pain), one item of the pain intensity subscale refers to the current moment (i.e., current pain), while all the items of the pain interference subscale refers to the last week. For the descriptive analyses, we used the mean subscale scores (i.e., total score / number of items responded). Both the scores of subscales for pain intensity and pain interference had the same theoretical range (although they have different amount of items) from 0 to 10. The German version of the BPI has shown good psychometric properties with good internal consistency, test-retest reliability, convergent validity, and construct validity (consistent with a two-factor structure).[33] In the current sample, the BPI subscales showed adequate internal consistency with Cronbach's alphas of .82 and .89 for intensity and interference subscales, respectively.

Procedure

As a standard procedure, patients completed a battery of questionnaires including the HADS and BPI at intake and discharge with the help of instructed research assistants. At intake, all participants provided informed consent for the use of their data for research purposes. The Ethics Committee of the Canton of Bern approved the study (project ID 2018-00493).

Analytic strategies

We conducted all the analyses using *R*.[34] Participants included in the analysis had completed at least one of the two measures used in this study at baseline. To deal with missing data, we used a random forest nonparametric multiple imputation strategy using the package *missForest*.[35]

Aim #1: Baseline Network of Depression, Anxiety, and Pain Symptoms. Based on the imputed sample, we ran an NA using the *R*-package *bootnet*.[36] In NA, the network

represents a pattern of relationships among the included symptoms. The different symptoms are named *nodes* and their relationships are called *edges*.[16] The edges could be positive or negative, implying direct or inverse associations between the elements of the network. Graphically, the nodes are represented by circles and the edges by lines connecting the circles. The thickness of the lines represents the strength of the association between the nodes. Furthermore, the color of the edges represents the nature of the association between the nodes, in terms of direct relationships (usually green or blue) or inverse relationships (usually red).

Mathematically, the network is formed based on calculating correlations between symptoms while controlling for the effects of other symptoms (i.e. partial correlations[37]). We used common regularization techniques to reduce the amount of weak edges as well as statistical criteria to select the network that best fits the data.[37] Thereby, the likelihood of spurious associations can be limited (i.e. false positives).[22,37] Thus, to estimate the partial correlations within the network, we used a regularization technique named 'graphical least absolute shrinkage and selection operator' (glasso).[38] As the glasso method provided several networks,[22] we used the Extended Bayesian Information Criterion to select the optimal network.[39] The EBIC has a hyperparameter (γ) set by the researcher to establish the degree, to which the criteria will prioritize sparser or more parsimonious networks. This value ranges from 0 to .5, with higher values implying simpler networks.[40] For this analysis, we set the γ parameter at .5, prioritizing the most parsimonious networks.[40]

Once we had identified the optimal network using this method, we calculated indices of symptom centrality within the network. Centrality is a measure of the connectivity of a symptom within the network, describing how well the symptom is associated to others in the network by estimating the likelihood that the presence (or intensity) of a symptom will trigger a systemic activation of the whole network.[41,42] Three main indices characterize centrality: Strength, closeness, and betweenness. *Strength* assesses how strong the connections among symptoms are.[43] A symptom with stronger connections has stronger associations with other

symptoms and might have a greater impact upon them (both positively and negatively). *Closeness* is a measure of distance between a specific symptom and all other symptoms in the network.[22] It is defined as the inverse of the sum of the shortest distance of one node from all the other nodes in the network.[43] Thus, a higher closeness means that a symptom has a shorter distance to other symptoms in the network. The effects of changes in symptoms with a high closeness are likely to spread more easily within the network.[22] Finally, *Betweenness* is a measure of how important a symptom is in terms of its connections with other symptoms.[43] A symptom with a high betweenness will often be in on the shortest path between other symptoms, linking one symptom to another. Betweenness is an important feature to identify symptoms that might function as *bridges* between symptoms or groups of symptoms within a network.[44]

We then checked the stability of the centrality indices by using bootstrapping procedures (2500 samples) and progressively dropping cases from the sample. Correlation stability (CS) indices (i.e. proportion of the sample that can be dropped maintaining a correlation of at least .70) above .50 are recommended.[36]

Considering recent concerns regarding the ability of centrality indices to identify relevant symptoms within a network,[45] we also calculated measures of nodes expected influence based on the formulas presented by Robinaugh, Millner, and McNally.[46] This method allows establishing two measures of expected influence. A one-step expected influence index that assesses symptoms influence with their direct neighbors, and a two-step expected index that measures both immediate and secondary influence of the nodes via their neighbors' further influences.[46]

To further establish symptom relevance within the network, we also ran a Minimum Spanning Tree (MST) analysis.[47] The MST produces a reduced network that connects all the edges with the minimum amount of them needed, providing insights into nodes' topological

relevance and hierarchical organization.[47,48] We run the MST analysis using the *ape* package.[49]

Aim #2: Baseline and Post-treatment Network Comparison. For comparison purposes we estimated an additional network with the symptoms measured at discharge, and compared both networks' general structure (i.e., the matrices of the networks' connection strength) and global strength invariance (i.e. the sum of all the weighted absolute edges' strength indices in the network) using the package *NetworkComparisonTest*.[50]

Aim #3: Comparison between Networks of Responders versus Non-Responders. We identified responders and non-responders to treatment and estimated a network for both samples at baseline and at post-treatment, using the IMMPACT[26] criteria described above. Once we identified the sample of responders and non-responders by this method, we again used the *NetworkComparisonTest* package to compare (i) the baseline networks of responders with non-responders and (ii) the baseline *versus* post-treatment networks in the group of patients who responded to treatment.

RESULTS

Sample descriptive statistics

Mean and standard deviation of all variables are displayed in Table 1, both at baseline and at post-treatment. The comparison of baseline and post-treatment levels by paired *t*-tests showed significant differences in three of the pain-intensity items, and in all pain interference, anxiety, and depression items (all suggesting a reduction in patients' severity). When adjusting the alpha level due to multiple comparisons using a Bonferroni correction, 20 out of the 25 items presented significant reductions during treatment. Of these, one anxiety symptom (i.e. restless) and two depression symptoms (i.e. appearance and enjoy TV) did not change significantly. Based on IMMPACT criteria, 229 (50.44%) presented a clinically relevant change during treatment (i.e., a reduction of half a standard deviation [.90 units] in BPI pain interference sub-scale).

Aim #1: Baseline Network of Depression, Anxiety, and Pain Symptoms

In Figure 1 we present a graphical representation of the estimated network grouped by the subscales of the items. The figure shows several associations between the item groups of pain interference and depressive symptoms. Although the pain interference nodes have associations with the anxiety symptoms (e.g. restless ↔ sleep, worrying ↔ mood, panic ↔ mood), they were weaker than the ones of depressive symptoms (e.g. [lack of being] cheerful ↔ mood, [lack of being] cheerful ↔ enjoyment, [lack of] laugh ↔ enjoyment). However, as it might be expected, there were several associations between anxiety and depression symptoms (e.g. relaxed ↔ slowed, tense ↔ slowed, worrying ↔ [lack of being] cheerful).

The pain intensity symptoms are presented apart from the whole network, they mostly do not have direct associations with anxiety or depression symptoms, but only with pain interference symptoms. The sleep node, from pain interference, is connected both with pain intensity (least and worst pain) and with anxiety nodes (being restless).

In synthesis, this means that most of the nodes associations were presented between pain interference and depression symptoms. Pain intensity nodes were only associated with pain interference nodes, being only indirectly associated to depressive and anxiety symptoms.

Centrality indices. Stability analyses of the centrality measures showed adequate CS indices for strength (.67) and closeness (.52), but a low CS index for betweenness (.21). The visual inspection of the CS plot (see Supplemental material 1, Supplemental Digital Content 1, http://links.lww.com/CJP/A613) showed consistent results, with stable correlations for strength and closeness (i.e. high level and slow reduction of the correlation when dropping cases) but unstable correlations for betweenness (i.e., low levels and steeper reductions in the correlations when dropping cases). In Figure 2, we present the distribution of the standardized centrality indices of strength and closeness (i.e., the indices that showed reliable results) for all the nodes in the network. The nodes with the highest strength centrality were [lack of] *laugh* (depressive symptom), *enjoyment-pi* (pain interference symptom; please note that there

is another enjoyment item within the depression symptoms, i.e. *enjoyment-d*), and *average* (pain intensity symptom). These nodes were the ones that presented the strongest connections within the network, having the greater impact upon the other network's nodes. The highest closeness scores were associated with *mood* (pain interference symptom), *enjoyment-pi* (pain interference symptom), and [lack of being] *cheerful* (depressive symptom)[a]. Thus, these nodes were the ones that presented the shortest distance with other nodes within the network, meaning that changes in them would spread more easily within the network.

Expected influence indices. We presented the results of the expected influences indices at Table 2. Consistent with the results of the centrality indices, the nodes with the greatest expected influence (both in one-step and two-step methods, ordered by ranking) where [lack of] *laugh* (depressive symptom), *enjoyment-pi* (pain interference symptom), and *average* (pain intensity symptom). *Mood* (pain intensity symptom) was the fourth node with greatest expected influence with the one-step method and the fifth node with greatest expected influence with the two-step method. The node [lack of being] *cheerful* (depressive symptom) was the fifth node with greatest expected influence with the one-step method and the fourth node with greatest expected influence with the two-step method. The results of these indices suggest that the symptoms [lack of] *laugh*, *enjoyment-pi*, *average*, *mood*, and [lack of being] *cheerful* are the ones with both greatest immediate influence (i.e., with their direct neighbors) and secondary influence (i.e., via their neighbors' further influences).

Minimum Spanning Tree Analyses. In Supplemental material 2, Supplemental Digital Content 2, http://links.lww.com/CJP/A614 we present the results of the minimum spanning tree analyses. The MST distribution is consistent with the observed baseline network

[a] We replicate these findings running exactly the same models but using standardized scores for the items, to control for any biased due to the differential ranges of the nodes[51]. The network estimated with this variation presented the same three nodes with the greatest centrality strength ([lack of] laugh, enjoyment-pi, and average) and closeness (mood, enjoyment-pi, and [lack of being] cheerful).

of Figure 1. In all cases, the items of the same sub-scales were grouped together. The main node connecting the branches of the MST (connecting with the depression, anxiety, and pain interference symptoms) and likely being central in the network is the [lack of being] cheerful item of the depression sub-scale. Overall, the MST showed that depression symptoms connected anxiety and pain symptoms (interference and intensity). Furthermore, pain intensity symptoms are connected to the network via pain interference symptoms. Thus, pain interference symptoms (especially enjoyment, mood, and sleep interference symptoms) also connected pain intensity and depression symptoms. Particularly, the pain interference symptom of sleep connects the pain interference symptoms with pain intensity nodes.

Aim #2: Baseline and Post-treatment Network Comparison

The test of network invariance between baseline and post-treatment data approached significance (*M* statistic = 0.21, $p = .065$). Additionally, the global strength invariance test showed a significant difference between the baseline and post-treatment networks (*S* statistic = 1.27, $p < .001$). The nodes from the baseline network presented a lower global strength (Mean = 10.60) than the nodes from the post-treatment network (Mean = 11.86). Thus, the global strength of the network tend to increase from baseline to post-treatment.

Aim #3: Comparison between Networks of Responders versus Non-Responders

When comparing baseline networks of responders versus non-responders we did not find a significant difference in the network structure (*M* statistic = 0.21, $p = .35$). However, there was a significant difference in networks' global strength (*S* statistic = 2.65, $p = .003$). The nodes in the non-responders' network showed a greater overall strength (Mean = 10.76) than the responders' network (Mean = 8.11).

Then, we compared the networks of responders at baseline with the same patients' networks at post-treatment. We did not find a significant difference between baseline and post-treatment network structure (*M* statistic = 0.20, $p = .54$). However, there was a significant difference in the networks' strength (*S* statistic = 4.20, $p < .001$). The nodes from

the responders' network at post-treatment had a greater overall strength (Mean = 12.31) than the baseline responders' network (Mean = 8.11).

DISCUSSION

The aim of the current study was to analyze the network structure of depression symptoms, anxiety symptoms, and pain severity indices in patients with chronic pain. We first ran a network analysis using baseline data from chronic pain patients. The results from the network analysis showed the greatest centrality and expected influence in the nodes [lack of] laughing, enjoyment (pain interference), average pain, [lack of being] cheerful, and mood. Second, we compared the network structure of the whole sample at baseline versus at post-treatment, finding that the post-treatment networks present a significantly greater node's strength compared to the baseline network. Thus, patients tended to increase their network strength during treatment. Third, we compared the baseline networks in responders *versus* non-responders and, in patients that responded to treatment, comparing baseline and post-treatment networks. The non-responders' network nodes presented a significantly greater strength than the responders' network. However, the responders' network at post-treatment had a significantly greater strength than the baseline responders' network. These results suggest that treatment non-responders tend to have a more strongly connected network at baseline, while responders tend to have weaker associations within their network. Nevertheless, the patients that respond to treatment tend to increase the strength of nodes association from baseline to post-treatment. To facilitate the comprehension of the findings we included a summary of the main results of the study in the Supplemental material 3, Supplemental Digital Content 3, http://links.lww.com/CJP/A615.

Baseline Network of Depression, Anxiety, and Pain Symptoms

Overall, the results of the network analyses at baseline showed that pain interference and depressive symptoms were most central. Consistently, in a network analysis in chronic pain, Thompson et al.[25] found that on the aggregate, the nodes for overall depressive

symptomatology and pain interference were the ones with greatest centrality. In the current paper, we used a more fine-grained symptom-level analysis rather than an overall sub-scale approach as the one of Thompson et al.[25], that allowed us to disaggregate specific symptoms within the estimated network and specify their single relevance. The symptoms with the greatest centrality (i.e., strength and closeness) in the network were the depressive symptoms of (not) laughing and (not) being cheerful, as well as the pain interference items of (lacking) enjoyment, and experiencing (negative) mood. These results were replicated by the node's expected influence analyzes.[46]

From a clinical standpoint, symptoms with a high strength and a high expected influence bear the promise to be good candidates for therapeutic targets,[11,46] because a change in these symptoms is more likely to have a greater impact on reducing other symptoms within the network of depression symptoms, anxiety symptoms, and pain symptoms.[24,52] For example, trying to help the patient to increase the number of enjoyable experiences in his or her life with a greater potential for (genuine) laughter may be a promising target being associated with greater changes in pain interferences. Also, the findings regarding closeness centrality indices may have important clinical implications. Because changes in symptoms with high closeness are more likely to spread more quickly within the network, symptoms with high closeness may also be promising therapeutic targets (especially if they have a substantive strength) and may be associated with a quicker systemic change by targeted interventions.[43] For example, as (not being) cheerful had high closeness indices within the network, interventions that help patients to experience more cheerful mood states are likely to have a more widespread beneficial impact on other network symptoms, particularly the pain interference experiences, compared to nodes with lower closeness scores.

Thus, the four items with greatest centrality (i.e., [lack of] laugh, [lack of being] cheerful, enjoyment, and mood) may produce the strongest and quickly spreading effects on the whole network if they are changed. Therefore, these four symptoms might represent prime

candidates for psychosocial interventions in the treatment of patients with chronic pain. However, this study represents only a first step in the identification of potential depressive/anxiety and pain symptoms that might be relevant targets for the treatment of chronic pain patients. Further research would be necessary to replicate these findings and identify sound symptom targets of clinical interventions for pain.

It is worth to highlight that the depressive symptoms presenting the greatest associations with pain interference and the greatest centrality and expected influence within the network describe the absence of positive psychological states (i.e. cheerful and laugh), and not only the presence of negative states. These results are in line with a growing body of research associating resilience resources with better coping strategies and attitudes towards chronic pain.[53,54] Specifically, positive affect, has been identified as a resilience mechanism associated with higher levels of coping responses, perceived self-efficacy and overall mental health in patients with chronic pain.[54,55] Furthermore, these findings might support the importance of following a *capitalization model* when treating chronic pain, that aims to work on activating the patients' strengths as the main mechanism of change (e.g., aiming to improve their capacities of being cheerful and having more humorous experiences), and not only a *compensation model* that focuses on modifying patients' deficits or vulnerabilities.[56,57]

The depressive symptoms also presented strong connections with the anxiety symptoms, partially linking anxiety symptoms with the rest of the network. These results are also consistent with those of Thompson et al.[25] at a construct level. Additionally, they are in line with a strong body of research indicating the close relationships between anxiety and depressive symptoms in terms of high rates of comorbidity[58], common etiopathogenesis[59,60] as well as the growing importance of unified protocols to treat them.[61,62]

Pain intensity items turned out to be separated from the other nodes of the network, being only connected with depression/anxiety symptoms via pain interference items. Particularly, sleep problems, from pain interference subscale, were both associated with pain

intensity and anxiety symptoms. It might be possible that higher pain intensity is particularly interfering and that anxiety symptoms were related if there are sleep problems involved. This is consistent with previous research showing associations between the intensity of chronic pain and sleep problems[63] as well as evidence suggesting a reciprocal relationship between both phenomena.[64] Thus, sleep problems might be a pivotal "connector" between pain intensity and anxiety, and may be potentially important for therapy or for prevention programs. These fine-grained symptom-level findings are also consistent with results by Thompson et al.[25] who reported that pain interference symptoms connect pain intensity with the whole network of symptoms. These findings might further support the relevance of interference pain symptoms for the multimodal treatment of chronic pain.

The MST analysis generally confirmed the above results and provided additional information on the differential topological relevance of the nodes in the network. Besides confirming some of the relationships among the groups of items (i.e. depression symptoms linking anxiety symptoms with the rest of the network and pain interference linking pain intensity with the whole structure), the MST highlighted the importance of (not being) cheerful as a core depressive symptom connecting pain interference, anxiety, and depression.

Baseline and Post-treatment Network Comparison

Whereas symptom distress scores were significantly reduced after treatment and the network structure remained relatively stable from pre to post treatment, the general strength of the associations among the nodes in the network *increased* over the rather short inpatient treatment (on average, three-weeks). The finding that the network structure remained stable from baseline to post-treatment has also been observed in other short-term interventions.[11] This might imply that the overall symptom structure cannot be modified substantially during a short-term multimodal inpatient treatment of chronic pain. The insignificant difference in the network structure between baseline and post-treatment symptoms is in line with this hypothesis, whereas this result should be interpreted extremely cautiously. The finding of an

increase in network strength from baseline to post-treatment also replicates previous studies showing an increase of item intercorrelations (i.e., higher connectivity in the network models) over time in different clinical settings.[11,52] This pattern has been consistent between different ranges of time (i.e., for 6 weeks to 2 years) and different sources of clinical information (patients self-reported and clinician-rated measures) and was also associated with a reduction of scale dimensionality and an increase in reliability within scales over time.[52] Although the authors of these papers explored several statistical and psychometric explanations (e.g., lack of normal distribution, floor or ceiling effects, spurious effects due to measurement bias), they refuted all of them because they did not fit their data, failing to find a likely cause to understand this finding.[11,52] Further research might need to replicate the finding of an increased network strength from baseline to post-treatment and continue exploring different statistical, psychometric, and clinical explanations and test them empirically, to fully understand the implications of this finding.

Comparison between Networks of Responders versus Non-Responders

The comparison between the baseline scores of responders *vs.* non-responders, and between the networks of responders at baseline vs. post-treatment suggests additional clinical implication for the treatment of chronic pain patients. On the one hand, patients who did not respond to treatment had a greater baseline strength of associations within the networks in comparison to patients who responded. This finding, consistent with previous theoretical and empirical studies[15,65], underlines the importance of evaluating patients' baseline network of symptomatic associations as predictor of treatment outcome, considering that having a strongly interconnected symptom structure at baseline seems to impede the success of a multimodal inpatient treatment for chronic pain. A more intense repeated-measures analysis of the associations between symptoms at baseline *within* each patient might not only provide personalized prognostic data (i.e. how hard it would be to produce changes in the patient) but

could also inform on likely profitable symptom targets for an *individual* patient[14], providing key information for personalized treatments of chronic pain patients.

As noted above, the comparison between responders' baseline and post-treatment networks showed an increase of the strength of the associations within the symptoms. In other words, whereas having looser symptom associations seems to facilitate symptom change during inpatient multimodal treatment for chronic pain, the symptom structure of successfully treated patients seems to consolidate over treatment. Understanding the quality of less pathological / more changeable symptom structures could provide further guidance to treatment development for chronic pain.

Limitations and Future Directions

Several limitations characterize this study. First, the study analyzed only chronic pain and depression/anxiety symptoms. Further psychopathological phenomena might be included to evaluate chronic pain syndrome networks in more detail (e.g. past adverse/traumatic events or personality disorder traits). The lack of a direct measurement of positive affect or resilience features related to chronic pain symptomatology, represents another limitation of the study. Future research might need to explore the associations among depression/anxiety symptoms, chronic pain symptoms, and other psychopathological as well as resilience phenomena in more detail. Second, we only analyzed cross-sectional data at two time points, i.e., at baseline and post-treatment, limiting the potential for deriving causal inferences in terms of symptoms associations. As a consequence, the observed relationships between the symptoms rather need to be interpreted as being interdependent over time. Following Granger's causality model[66,67], future studies might need to implement a more intensive repeated-measure assessment of depression/anxiety symptoms and chronic pain symptoms, with methods like Ecological Momentary Assessment[68], evaluating cross-lagged associations among symptoms. Third, we only analyzed a short-term three-week inpatient treatment for chronic pain. The short-term nature of the treatment might limit the possibility of finding structural differences between

baseline and post-treatment networks. Further research, analyzing treatments for chronic pain that may also include day-hospital or outpatient treatments, might provide stronger evidence for the structural evolution of symptom networks during chronic pain treatment. Fourth, the low stability of the betweenness centrality index limited us in the possibility of drawing robust conclusions on relevant symptoms in terms of mediated relationships among symptoms. Finally, the network analysis was focused only on analyzing symptom-level and symptom-interference nodes. Whereas this data might inform clinical practice from a psychopathological perspective (i.e. symptoms and symptom-interferences that are relevant within the network), it does not inform about other clinically and therapeutically relevant variables that are associated both with the network and change during treatment, e.g. patient expectations or motivation to treatment.

Besides these limitations, this study provides relevant information on pain, depression, and anxiety symptoms associations in patients with chronic pain. Furthermore, the findings have the potential to inform treatment development, particularly supporting a capitalization approach to chronic pain treatment to improve depressive and pain interference features.

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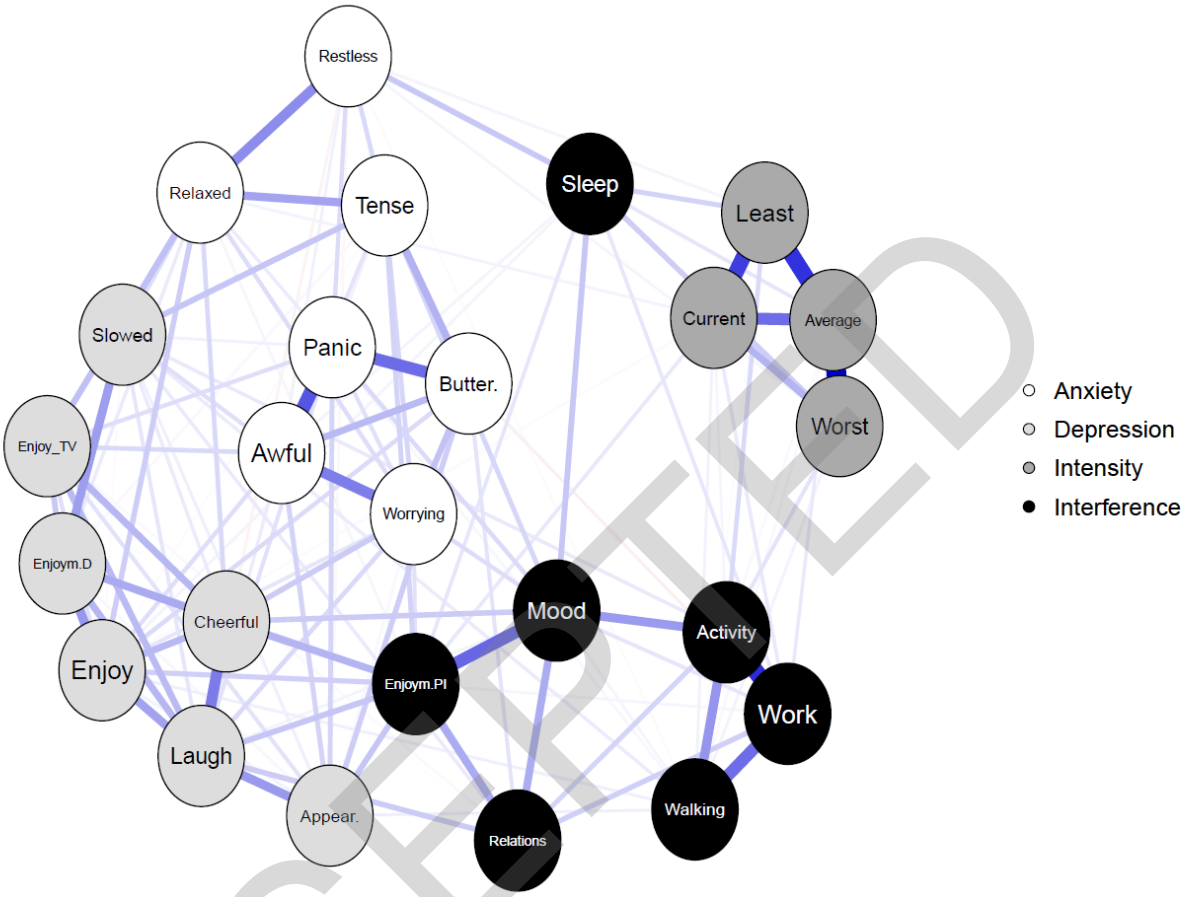
Figure legends

FIGURE 1. Network analysis of the association among pain and depressive/anxiety symptoms. Note. Enjoym.PI = Enjoyment (Pain Interference sub-scale), Enjoym.D = Enjoyment (Depression sub-scale), Appear. = Appearance (Depression sub-scale), Butterf. = Butterflies (Anxiety sub-scale), Enjoy_TV = Enjoy television. All the edges in the Figure are positive, with the exception of Restless <-> Walking, Restless <-> [lack of] Laugh, Restless <-> Appearance, and Butterflies <-> Walking.

FIGURE 2. Standardized centrality indices for the baseline network of pain and depressive/anxiety symptoms.



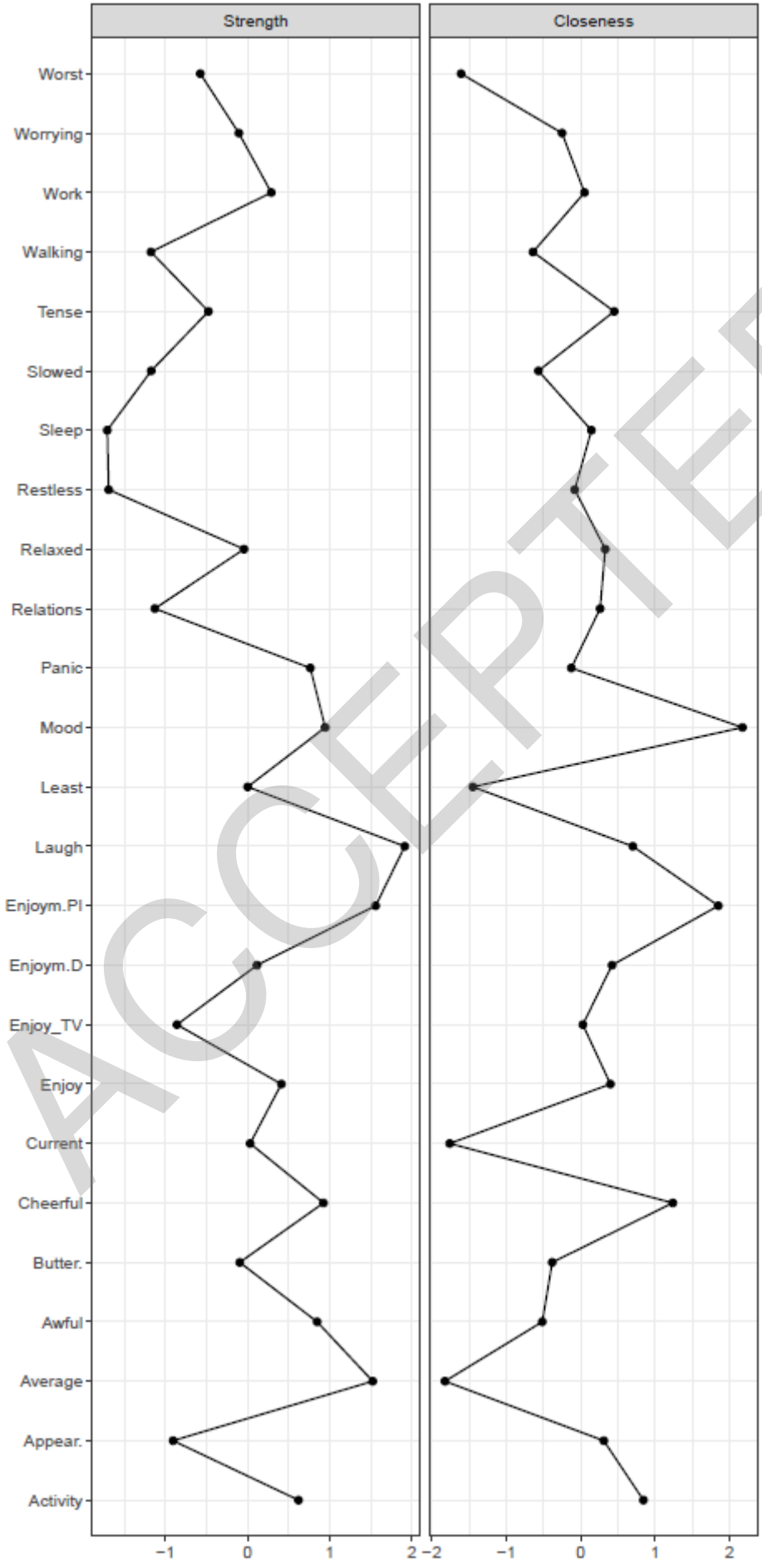


TABLE 1. Descriptives and mean comparison of pain and affective symptoms at baseline and post-treatment

	Baseline (n = 454)		Post-treatment (n = 335)		Baseline to Post-treatment differences	
	M	*SD*	*M*	*SD*	$t(273/334)^a$	*p*
Pain Intensity	5.60	1.84	5.25	2.02	3.33	.001
Worst	7.45	1.99	6.89	2.22	4.77	< .001
Least	3.86	2.16	3.71	2.25	0.41	.68
Average	5.72	1.92	5.24	2.09	4.20	< .001
Current	5.36	2.36	5.15	2.38	0.66	.51
Pain Interference	5.97	1.90	4.86	2.17	10.30	< .001
Activity	6.57	2.39	5.44	2.50	7.21	< .001
Mood	6.09	2.76	4.98	2.74	6.63	< .001
Walking	5.15	3.14	4.29	2.99	4.60	< .001
Work	6.72	2.49	5.57	2.73	6.22	< .001
Relations	5.05	3.15	3.65	2.98	7.04	< .001
Sleep	6.31	3.12	5.41	3.21	5.04	< .001
Enjoyment-PI	6.02	2.98	4.54	2.98	8.99	< .001
Anxiety	1.52	0.64	1.21	0.66	10.66	< .001
Tense	1.89	0.95	1.28	0.87	10.98	< .001
Awful	1.41	1.20	1.13	1.11	3.70	< .001
Worrying	1.74	1.01	1.36	1.01	6.92	< .001
Relaxed	1.78	0.91	1.44	0.89	6.77	< .001
Butterflies	1.25	1.02	1.02	0.94	3.42	.001
Restless	1.49	1.06	1.34	0.94	2.87	.004
Panic	1.17	1.01	< .001	0.89	4.69	
Depression	1.42	0.67	1.10	0.67	11.07	< .001
Enjoy	1.61	1.06	1.11	0.90	8.99	< .001
Laugh	1.25	.91	0.88	0.84	7.04	< .001
Cheerful	1.43	.97	1.12	0.97	6.03	< .001
Slowed	2.19	.91	1.75	0.90	8.31	< .001
Appearance	1.00	1.07	0.86	1.00	2.07	.039
Enjoyment-D	1.58	1.02	1.18	0.96	8.05	< .001
Enjoy_TV	0.98	1.02	0.78	0.88	3.16	.002

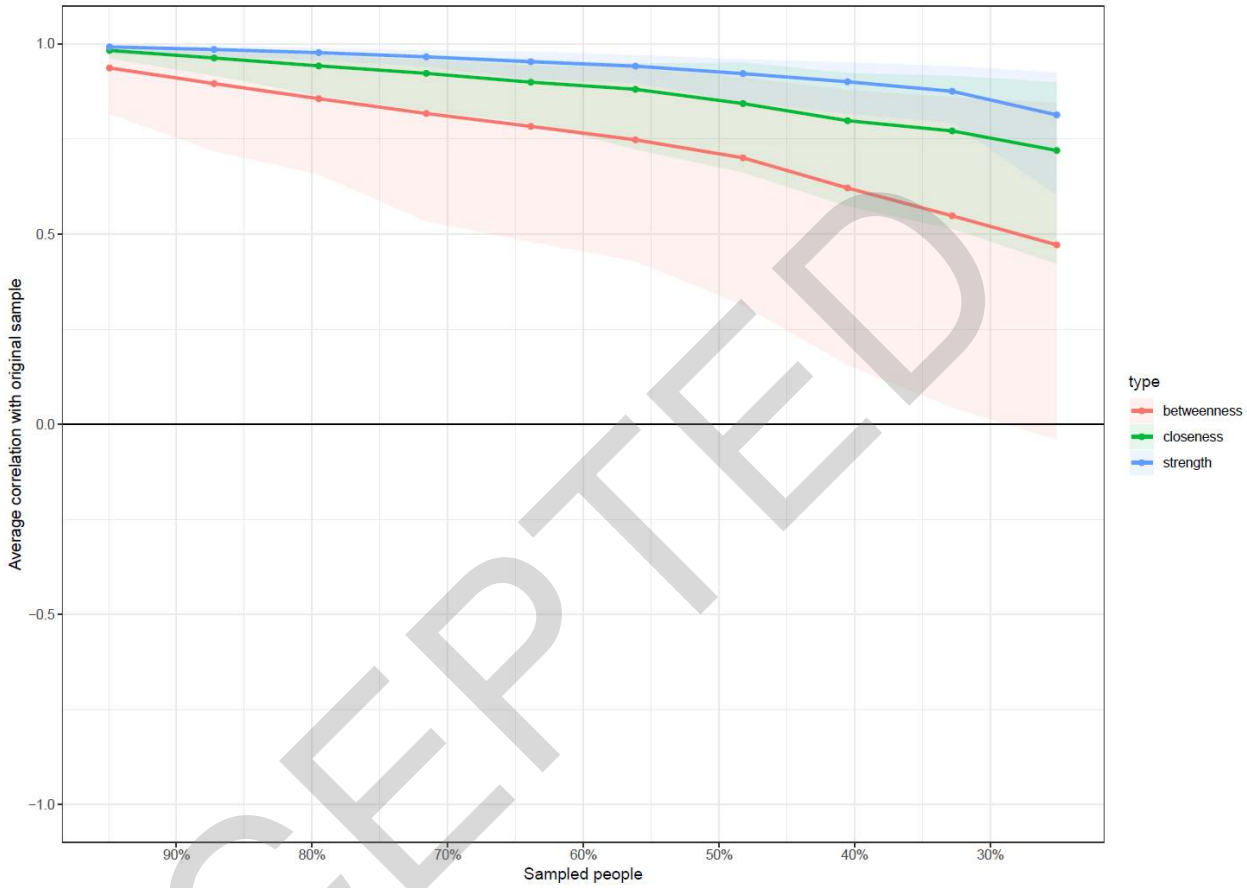
Note: [a] Paried *t*-tests for pain symptoms had 273 degrees of freedom, while the paired *t*-tests for anxiety/depressive symptoms had 334 degrees of freedom. A Bonferroni correction for multiple comparion (i.e. α / 25) set the alpha at a .002 level.

TABLE 2. One- and two-step expected influence of network's nodes

	Dimension	One-step expected influence (EI_1)	EI_1 rank	Two-step expected influence (EI_2)	EI_2 rank
Worst	Pain Intensity	0.77	18	1.55	15
Least	Pain Intensity	0.88	13	1.75	11
Average	**Pain Intensity**	**1.19**	**3**	**2.18**	**3**
Current	Pain Intensity	0.89	11	1.75	12
Activity	Pain Interference	1.01	8	1.86	9
Mood	**Pain Interference**	**1.08**	**4**	**2.09**	**5**
Walking	Pain Interference	0.63	23	1.21	23
Work	Pain Interference	0.89	12	1.65	14
Relations	Pain Interference	0.65	21	1.34	21
Sleep	Pain Interference	0.54	24	1.01	24
Enjoyment-PI	**Pain Interference**	**1.20**	**2**	**2.30**	**2**
Tense	Anxiety	0.79	17	1.47	18
Awful	Anxiety	1.06	6	1.97	6
Worrying	Anxiety	0.86	15	1.73	13
Relaxed	Anxiety	0.87	14	1.54	17
Butterflies	Anxiety	0.81	16	1.55	16
Restless	Anxiety	0.45	25	0.82	25
Panic	Anxiety	1.03	7	1.95	7
Enjoy	Depression	0.97	9	1.91	8
Laugh	**Depression**	**1.23**	**1**	**2.34**	**1**
Cheerful	**Depression**	**1.07**	**5**	**2.14**	**4**
Slowed	Depression	0.65	22	1.23	22
Appearance	Depression	0.67	20	1.36	20
Enjoyment-D	Depression	0.91	10	1.77	10
Enjoy TV	Depression	0.71	19	1.42	19

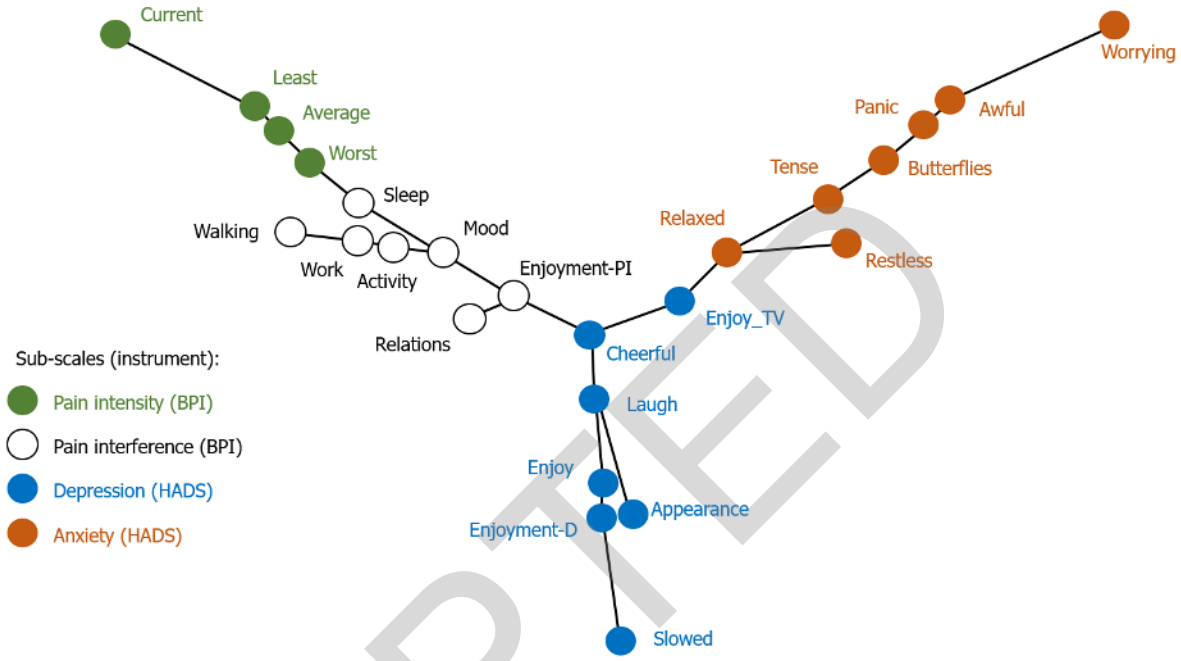
Note: The first five nodes with the greatest expected influence are in bold.

Supplemental material 1



SUPPLEMENTAL MATERIAL 1. Correlation stability plot from the centrality indices.

Supplemental material 2



SUPPLEMENTAL MATERIAL 2. Minimum spanning tree differentiating nodes by sub-scales.

Supplemental material 3

SUPPLEMENTAL MATERIAL 3. Summary of the main results of the study

Baseline network

Correlation stability of the centrality indices

Strength = .67 / *Closeness* = .52 / *Between* = .21

Nodes with greatest strength centrality

Laugh / *Enjoyment-PI* / *Average pain*

Nodes with greatest closeness centrality

Mood / *Enjoyment-PI* / *Cheerful*

Nodes with greatest one-step expected influence

Laugh / *Enjoyment-PI* / *Average pain*

Nodes with greatest one-step expected influence

Laugh / *Enjoyment-PI* / *Average pain*

Minimum spanning tree most central nodes

Cheerful / *Laugh* / *Enjoyment-PI*

Baseline and post-treatment network comparison

Global strength

Baseline mean strength = 10.60

Post-treatment mean strength = 11.86

S statistic = 1.27, $p < .001$

Responders versus non-responders baseline network comparison

Global strength

Non-responders baseline mean strength = 10.76

Responders baseline mean strength = 8.11

S statistic = 2.65, $p = .003$

Responders baseline and post-treatment network comparison

Global strength

Baseline responders mean strength = 8.11

Post-treatment responders mean strength = 12.31

S statistic = 4.20, $p < .001$

Note. We included the first three nodes with greatest centrality in each centrality index. PI = Pain interference.