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Title:

The relationship between demoralization and depressive symptoms among patients from the general hospital: network and exploratory graph analysis

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Abstract

Introduction. Depression and demoralization are highly prevalent among individuals with physical illnesses but their interrelationship is still unclear.

Objective. To examine the relationship between clinical features of depression and demoralization with the network approach to psychopathology.

Methods. Participants were recruited from the medical wards of a University Hospital in Italy. The Demoralization Scale (DS) was used to assess demoralization, while the Patient Health Questionnaire-9 (PHQ-9) to assess depressive symptoms. The structure of the depression-demoralization symptom network was examined and complemented by the analysis of topological overlap and Exploratory Graph Analysis (EGA) to identify the most relevant groupings (communities) of symptoms and their connections. The stability of network models was estimated with bootstrap procedures and results were compared with factor analysis.

Results. Life feeling pointless, low mood/discouragement, hopelessness and feeling trapped were among the most central features of the network. EGA identified four communities: (1) Neurovegetative Depression, (2) Loss of purpose, (3) Frustrated Isolation and (4) Low mood and morale. Loss of purpose and low mood/morale were largely connected with other communities through anhedonia, hopelessness and items related to isolation and lack of emotional control. Results from EGA displayed good stability and were comparable to those from factor analysis.

Limitations. Cross-sectional design; sample heterogeneity

Conclusions. Among general hospital inpatients, features of depression and demoralization are independent, with the exception of low mood and self-reproach. The identification of symptom groupings around entrapment and helplessness may provide a basis for a dimensional characterization of depressed/demoralized patients, with possible implications for treatment.

Keywords: depression; demoralization; physical illness; anhedonia; coping; entrapment; helplessness

1. Introduction

Depression and demoralization are highly prevalent among individuals with physical illnesses but their interrelationship is still partly unclear (Nanni et al., 2018a, 2018b; Robinson et al., 2016a; Tecuta et al., 2015; Thom et al., 2019). In particular, the question remains whether they are part of one dimensional concept with different tendencies for expression, or do they have distinct features that interact in complex and mutually influential ways.

The expression of depressive symptoms in the medically ill can vary between those reflecting adjustment and full-fledged mood disorders, which is problematic and has profound implications for clinical management (e.g. decision whether to initiate psychotropic medication, psychotherapeutic treatment or both) (Bachem and Casey, 2017; Grassi et al., 2007; Maercker and Lorenz, 2018). Most available research on this topic relies on the use of formal diagnostic categories, such as depressive, anxiety or adjustment disorders, that are usually defined according to DSM criteria (American Psychiatric Association, 2013) or the most recent ICD-11 (Glaesmer et al., 2015). Here, in order to reach the diagnostic threshold an individual is required to display a predefined number of symptoms drawn from a non-exhaustive list, which often comprises psychological, cognitive as well as physical phenomena (Fried, 2017; Kendler, 2017, 2016). Disagreement can occur between researchers on the utility of these criteria when applied in medical settings (Thom et al., 2019; von Ammon Cavanaugh, 1995; Walker et al., 2018).

Likewise, demoralization has been largely studied in oncology and palliative care (Grassi and Nanni, 2016; Nanni et al., 2018a; Robinson et al., 2016a; Tang et al., 2015; Tecuta et al., 2015), as well as in other medical settings (Belvederi Murri et al., 2015; Mangelli et al., 2005; Marchesi and Maggini, 2007; Raviola et al., 2002). Demoralization is envisioned as a mental state characterized by a combination of distress (low morale, sadness, discouragement, and resentment) and poor coping (feelings of being trapped or stuck because of a sense of inability to plan and initiate concerted action toward one or more goals), which determine feelings of pointlessness, helplessness and hopelessness. Although it is often assessed as a continuous trait, it was recently proposed as a specifier of adjustment disorder or depression, given its clinical relevance, treatment specificity and detrimental consequences in inducing suicidality (Kissane et al., 2017).

The issue of whether depression and demoralization should be considered distinct clinical entities is still debated. They present several clinical features (symptoms) in common, such as low mood, pessimism or low self-esteem, with observed rates of comorbidity. Studies show that physically ill subjects who are highly demoralized often fulfil the criteria for major depression and vice versa (Mangelli et al., 2005). This is particularly evident for severe demoralization, but less so for moderate demoralization, where the phenomenology of poor adjustment is expressed as demoralization. In addition, these conditions predict each other in the longitudinal perspective (Robinson et al., 2015), suggesting a reciprocal dynamic relationship and further complicating their distinction. Various authors have attempted to distinguish between depression and demoralization from a categorical (de Figueiredo, 1993; Wellen, 2010) or dimensional perspective (Bobevski et al., 2018; Clarke et al., 2002; Guidi et al., 2011). Some have argued that the hallmark of demoralization is subjective incompetence, whereas anhedonia and loss of motivation would mainly characterize depression; however, disagreement persists, for instance, on whether neurovegetative symptoms may be specific to depression or present also in demoralization (Clarke and Kissane, 2002; de Figueiredo, 2013, 1993; Wellen, 2010). Biologically, hope and morale employ dopamine circuits projecting from the prefrontal cortex to the nucleus accumbens, whereas mood circuits employ serotonergic and noradrenergic pathways projecting from the prefrontal cortex to the amygdala and hippocampus (Leach, 2018; Nestler et al., 2009). Overall, it seems reasonable to assume that the boundaries between depression and demoralization are blurred.

The relationship between demoralization and depression can be successfully explored in the context of the network approach to psychopathology (Cramer et al., 2010; Fried, 2015). Unlike the “common cause” theoretical model, whereby a disorder/disease *causes* a set of symptoms, (e.g. lack of insulin causes several distinct clinical features of diabetes), the network *theory* of mental disorders conceives disorders as complex system emerging from mutually interacting symptoms (Borsboom, 2017; Contreras et al., 2019; Fried and Nesse, 2015). In the network approach, symptoms are represented as nodes, connected by edges of varying width; the connections, in turn, represent the strength of their causal relationships. In this view, unrelated disorders would be represented by distinct, unconnected networks of symptoms. Whereas, comorbid disorders may present as overlapping networks, i.e. sharing one or more nodes, some of which could work as “bridges” (Borsboom et al., 2016; Cramer, 2012; Cramer et al., 2010).

Network psychometrics is a rapidly-evolving, overarching analytic approach to examine the structure/organization of psychological disorders (Contreras et al., 2019; Robinaugh et al., 2020). Starting from clinical data, it is possible to identify the more meaningful connections between individual symptoms, within or across disorders, thus highlighting the phenomenological pathways that are more likely to lead from one disorder to another (Cramer et al., 2010). The integration of network and latent factor approaches, in particular, seems particularly promising to explore the structure of related disorders (Christensen and Golino, 2020; Epskamp et al., 2017; Hallquist et al., 2019; van Bork et al., 2019). A recent, intriguing development in this sense is Exploratory Graph Analysis (EGA) (Golino and Christensen, 2020; Golino and Epskamp, 2017). EGA allows one to identify the groupings of symptoms (“*communities*”, or dimensions) that are more strongly connected in the symptom network, which indicate greater relatedness and, possibly, similar pathogenetic mechanisms. This methodology has been employed to investigate the structure of psychopathology in various domains (Christensen et al., 2018; Forkmann et al., 2018; Golino and Demetriou, 2017). Thus, within network psychometrics, EGA seems particularly suited to explore the interactions between symptoms of depression and demoralization and their mutual relationships (Eaton, 2015; Golino and Christensen, 2020).

Given these premises, the aim of this study was to examine the relationship between clinical features of depression and demoralization among physically ill individuals, using the network approach and EGA. In particular, we aimed at examining the network of depression and demoralization symptoms, highlighting the overlap and relative importance of individual symptoms, their groupings and reciprocal interactions. We hypothesized that the majority of symptoms of depression and demoralization would segregate into distinct communities, particularly neurovegetative symptoms and items related to poor coping, whereas, we expected that shared features of depression and demoralization (e.g. depressed mood and death thoughts) would be aggregated in the same communities.

2. Material and Methods

2.1 Study sample

This study is based on data relative to the prevalence and characteristics of demoralization in the general hospital, as presented elsewhere (Belvederi Murri et al., 2019). Briefly, participants were recruited from medical wards (internal medicine, cardiology, endocrinology, nephrology, gastroenterology, pneumology, rheumatology and oncology) of the Sant'Anna University Hospital in Ferrara, Italy. Patients were eligible according to the following criteria: (1) age ≥ 18; (2) clinical condition compatible with responding to the clinical interview, e.g. absence of delirium and/or severe cognitive impairments; (3) fluency in the Italian language. After removal of subjects with missing data (n=26), a total of 447 subjects comprised the study sample. Patients were asked to complete self-report questionnaires and underwent a semi-structured interview with residents in Psychiatry or researchers with specific experience in psychosomatic medicine. Subjects provided informed consent, and the study was approved by the Ethical Committee at the local institution.

2.2 Measures

The Demoralization Scale in its 24-item version (DS) was developed to assess symptoms of demoralization in the past two weeks among patients with cancer (Grassi et al., 2017; Kissane et al., 2004). The Italian validated version of the DS showed four factors: Loss of Meaning and Purpose, Dysphoria, Disheartenment and Sense of Failure (Grassi et al., 2017). Respondents are asked to rate the frequency of each symptom in the past two weeks using a 5-point Likert Scale (0 = never; 4 = all the time). A cut-off score of 30 or higher has shown good reliability with the presence of demoralization (Nanni et al., 2018a).

The Patient Health Questionnaire-9 (PHQ-9) was used to rate the frequency of depressive symptoms in the past two weeks, using a 4-point Likert scale (0, Not at all; 1, Several days; 2, More than half the days; 3, Nearly every day). The PHQ-9, in its Italian validated version, showed good psychometric properties (Kroenke et al., 2001; Thombs et al., 2014) and has been extensively used in the medical setting to establish the presence of major depression according to DSM–IV criteria, using a cutoff value of 10 points or higher (Gilbody et al., 2007; Moriarty et al., 2015).

2.3 Data analysis

We first report descriptive analyses for the sample and reliability analyses for the rating tools. For the latter we provide estimates of the Omega index (Peters, 2014) calculated with the *userfriendlyscience* package assuming ordinal levels (Peters, 2018).

2.3.1 Network estimation

Exploratory Graph Analyses follow the estimation of the network structure according to a Gaussian Graphical Model (Epskamp et al., 2012). We expected some degree of overlap between symptoms of depression and demoralization, which is also reflected by some similarities in the wording of items of the PHQ-9 and the DS. Including nodes with high similarity in the same network can artificially inflate their centrality, given the presence of strong intercorrelations between them; this issue is known as "topological overlap" (Contreras et al., 2019). Thus, we sought to examine the weighted topological overlap of items using the *node.redundant* function of the EGAnet package 0.9.3 (Golino and Christensen, 2020). This function allows one to visually inspect the local network of potentially redundant nodes, and to combine those displaying greater overlap into distinct latent factors using the *node.redundant.combine* function. To this end, we aimed at combining only items displaying both topological overlap and high conceptual similarity. The resulting features were used to estimate the network of depression and demoralization.

The network estimation is based on regularized partial correlations among variables, which index the strength of the association between each pair of items, while controlling for all other associations in the network. The Graphical Least Absolute Shrinkage and Selection Operator (GLASSO) procedure then selects the stronger set of connections, thus reducing the risk of detecting false-positive associations and obtaining a *sparse* network. The weight adjacency matrix reports the numerical values of conditional dependence relationships between all items, while the network is visualized graphically using the Fruchterman-Reingold algorithm (Epskamp et al., 2018). We report on the centrality measure of *Strength*, indicating the sum of the weight of all direct connections between each symptom and the others (Borsboom and Cramer, 2013; Bringmann et al., 2019), and recently appraised as being statistically equivalent to latent factor loadings (Christensen and Golino, 2020). The stability of node strength was estimated using a case dropping bootstrap procedure (1000 iterations) as provided in the package *bootnet 1.3* (Epskamp et al., 2018): this procedure allows estimation of any modifications of strength and edge weights after dropping an increasing proportion of cases from the sample. All analyses were performed using R version 3.6.3 (R Core Team, 2020)

2.3.3 Exploratory Graph Analysis

Communities are clusters of nodes that are highly connected with one another, but only modestly with the nodes within other clusters (Cramer et al., 2010). To identify the communities of symptoms we used Exploratory Graph Analysis (EGA) based on the Gaussian graphical model as calculated in the *EGAnet* package, version 0.9.4 (Golino and Christensen, 2020). EGA is based on the walktrap algorithm, which allows to identify a discrete number of dense subgraphs (communities) by performing a series of random walks across the nodes in the network. This procedure was repeated in 10,000 non-parametric bootstrap iterations using the *bootEGA* function to estimate the median number of communities and their symptom composition (Christensen and Golino, 2019). The stability of such results is estimated in terms of replication across the bootstrap iterations. In particular, item replication is the proportion of bootstraps where each item appeared in each possible dimension. High values suggest that the item is consistently identified in such dimension, low values that the item might be multidimensional. Dimension stability is proportion of times the original dimension is exactly replicated across bootstrap samples (Golino and Christensen, 2020).

Lastly, to gauge information on the role of single items in each community, we report the values of *network loadings*, calculated as the standardized strength of the connections between each node and the others within the same community (dominant) or in other communities (cross-dimensional) (Christensen and Golino, 2020; Golino et al., 2020).

2.3.3 Latent variable approach: comparison with exploratory factor analysis

Previous studies showed that EGA was as effective, or more effective than other analytic techniques in recovering the number of dimensions underlying psychometric data (Golino et al., 2020; Golino and Epskamp, 2017). However, given the novelty of EGA and the limited sample size, we deemed it useful to compare its results with those obtained from factor analysis, used as the benchmark method. Using the *psych* package (Revelle, 2018) we established the optimal number of factors with parallel analysis in 1000 resampling iterations. Then we conducted an Exploratory Factor Analysis (EFA) of DS and PHQ-9 item data with Maximum Likelihood estimation and Varimax rotation. The fitness of EGA and EFA-derived models were finally compared evaluating the Total Entropy Fit Index, where lower values indicate better fit of the model (Golino et al., 2019). In addition, we report the corresponding latent factor model of the EGA structure, obtained using the *CFA* function from the EGAnet package.

3. Results

3.1 Population characteristics

The majority of participants were females, with a mean age of 62 (Table 1). Table 1 also reports the prevalence of endorsement of severe symptom values for each item of the PHQ-9 and DS, along with complete item wording. Henceforth, only abbreviated captions are used for brevity.

The cross-tabulation of subjects displaying depression and demoralization, according to predefined cutoff of the DS and PHQ-9, revealed that a large proportion of subjects were neither depressed, nor demoralized (n=212, 47.4%), while 34.7% (n=155) were both depressed and demoralized. In the remainder of the sample, fifty-three subjects displayed only demoralization, but not depression (11.9%) or displayed depression, but not demoralization (n=27, 6.0%).

Reliability of the scales were excellent for the DS (Omega: 0.95; 95%CI: 0.95 - 0.96) and good for the PHQ-9 (Omega: 0.88; 95%CI: 0.86 - 0.90). Joined data from both questionnaires was also highly reliable (Omega: 0.96; 95%CI: 0.96 - 0.97).

3.2 Estimation of node redundancy

Potential topological overlap was revealed among eleven groups of items, for a total of 28 items. Sixteen items from the DS and the PHQ-9 were judged to be also conceptually overlapping, thus were combined into six latent factors (*mood/discouragement, guilt/lack of pride, lack of purpose, death ideation, lack of value, irritability/anger*, see Table S1 for details). Whereas, 12 items were indicated as potentially overlapping, but were not combined owing to their conceptual distinction. Thus, out of 33 items, a final set of 23 variables were entered in the network.

3.3 Network of demoralization and depressive symptoms

The network of depression and demoralization is reported in Figure 1, depicting the connections between individual features and the communities of symptoms. The most central items in the network (Figure S1) were *life pointless* (DS 2), mood/discouragement (latent factor), *hopelessness* (DS 9), *entrapment* (DS 24), *feeling bad about self* (PHQ 6), *lack of interest/pleasure* (PHQ 1), *lack of concentration* (PHQ 7) and *isolation* (DS 23), whereas *sleep* and *appetite problems* (PHQ 3 and 5) were the least central (Figure S1).

Table S2 in the Supplement reports the values of edge weights in the network. The strongest connections were between *life pointless* (DS 2), *lack of purpose* (latent factor) and *hopelessness* (DS 9); between *helplessness* (DS9) and *isolation* (DS23), between *hopelessness* (DS 9) and death ideation (latent factor), between *irritability-anger* (latent factor) and *being easily hurt* (DS 11), between *inability coping* (DS 9) and *lack of value* (latent factor), between *entrapment* (D24) and *distress* (D18); between *lack of interest/pleasure* (PHQ1) and *tiredness* (PHQ 4); between *tiredness* (PHQ 4) and *appetite problems* (PHQ 4), between *lack of concentration* (PHQ7) and *slowing/agitation* (PHQ8).

The stability of node strength in the network was good (Figure S2 in the Supplement): 80.8% of the sample could be dropped maintaining a correlation of 0.76 (SD 0.03) between the new values of node strength and those from the original sample (CS-C coefficient), and a correlation of 0.69 (SD 0.04) for edge weights.

3.4 Exploratory Graph Analysis

After 10,000 bootstrap procedures, the EGA revealed the presence of a median of four communities in the network in 72.5% of the bootstrap iterations (95% CI 2.9 – 5.1). The item composition of each community is reported in Table 2, along with the values of item replication. The first community, termed "*neurovegetative depression*" comprised items 1, 3, 4, 5, 7, and 8 from the PHQ. The second community, "*loss of purpose*", comprised the latent factors *lack of purpose, death ideation* and *lack of value*, as well as items 2, 9, 12 and 8 from the DS. The third, "*frustrated isolation*" comprised the latent factors *guilt/lack of pride* and *irritability/anger,* as well as items 7, 15, 21, 5 from the DS and item 6 from the PHQ. The fourth community, *"low mood/morale"* comprised the latent factor *mood/discouragement* and items 18 and 24 from the DS.

The composition of community 4 replicated exactly in 82.4% of the bootstrap iterations (dimension stability), followed by community 3 (78.5%), community 2 (52.6) and community 1 (39.3%). Also, assignment of single items to communities was quite reproducible (Table 2 and Figure 2): values indicated high probability of replicating in the indicated community across the bootstrap procedure, except for three (anhedonia, sleep disorders and "can't help oneself").

As expected, within-community connections were stronger than connections between symptoms belonging to different communities. Several highly-central symptoms also had non-negligible cross-dimensional network loadings (pointless, hopelessness, bad-self, mood discouragement, see Table S3). More specifically, community 1 was connected to community 2 by the edge between *lack of interest/pleasure* and *life pointless* and to community 4 mostly by the edge between *lack of interest/pleasure* and *mood/discouragement.* It only displayed weaker connections with community 3. In addition, community 2 was connected to community 3 by the edges between *life pointless* and *isolation*, *life pointless* and *helplessness*; and to community 4 by the edges between *hopelessness* and *distress*, *hopelessness* and *mood/discouragement, hopelessness* and *entrapment.* Community 3 was also connected to community 4 by the edges between *lack of emotional control* and *mood/discouragement, and between isolation* and *mood/discouragement.*

3.5 Comparison with factor analysis

The set of connections yielded by EGA was converted into a latent variable model for inspection (Figure S3 in the Supplement). The Total Entropy Fit Index was -13.16. Data were also analysed with exploratory factor analysis. Parallel analysis also suggested the extraction of four factors. Table S4 reports the composition of latent factors, which were largely comprised of similar items to community. In particular factor 2 comprised two items that were placed in community 1 (*tiredness* and *lack of interest/pleasure*), and one item that was placed in community 2 (*can't help oneself*). This model had similar fit to the EGA-derived model (TLI: 0.95, RMSEA: 0.049, 90%CI: 0.042 - 0.057, BIC: -670.29, TEFI = -13.55, Table S5).

4. Discussion

This study examined the relationship between demoralization and depression in a sample of patients recruited from the general hospital, using the network approach to psychopathology. Results suggest that features of depression largely segregate in different communities from those of demoralization, with the exception of low mood/morale, death wishes and self-reproach. EGA was as reliable as factor analysis in identifying the relative clustering of symptoms and in identifying the pathways of reciprocal influence in the symptom network.

Depression and demoralization are frequently comorbid and display overlapping symptoms (Bobevski et al., 2018; Clarke et al., 2002; Robinson et al., 2015; Tecuta et al., 2015). Using EGA, within the network approach to psychopathology, we explored the groupings of their symptoms while highlighting their most relevant interconnections. This methodology allows us to draw inference on the strength of the relationship between each pair of symptoms, while adjusting for the influence of all other nodes in the network (Borsboom, 2017; Golino and Epskamp, 2017). According to the network view on comorbidity, symptoms that overlap between two distinct, often comorbid disorders, may be particularly important to explain their co-occurrence and reciprocal influence (Afzali et al., 2017; Cramer et al., 2010) as well as explaining the patterns of mixed clinical pictures (Cramer et al., 2010). Results suggest that lack of interest, somatic and cognitive symptoms, which represent specific features of depression, were all grouped within the same community. These findings are in line with the observations of other authors, indicating anhedonia (particularly *consummatory* pleasure), lack of concentration, insomnia, anergia or appetite changes as characteristic features of depression, but generally absent from demoralization (Clarke et al., 2002; de Figueiredo, 1993; Wellen, 2010). In the study population, somatic symptoms of depression may be directly influenced by the presence of physical illnesses, such as diabetes, cardiovascular disease or COPD, which may exert direct effects on sleep, appetite, energy levels, motor functions and concentration (Gleason et al., 2013; Goodwin, 2006; Krishnan et al., 2002). Consistent with another recent study on late life depression (Belvederi Murri et al., 2018a), somatic symptoms were rather peripheral in the network of depression and demoralization, and may arguably serve as “bridge” symptoms that trigger the onset of depression from symptoms related to physical diseases (Kapfhammer, 2006). In this regard, anhedonia may represent a critical hub, as it represented the main connection between the “neurovegetative” cluster and the “low mood/morale” cluster. Anhedonia is often associated with low energy, altered sleep and appetite as part of the clinical picture of “sickness behavior”, and may depend, at least in part, on biological mechanisms (Anderson et al., 2014; Dantzer et al., 2008; Lee et al., 2018; Swardfager et al., 2016).

Symptoms of demoralization segregated into three, distinct communities, consistent with its recognized multidimensional nature (Robinson et al., 2016a). They were intertwined (and two of them actually combined) with depressive symptoms such as *low mood/morale, death wishes* and *self-reproach*, with whom they show the largest degree of content overlap (Clarke et al., 2002; de Figueiredo, 1993; Wellen, 2010). In particular, the community we named “*low mood and morale*” was directly connected with all other communities and comprised different emotions that are found in both demoralization and depression (Wellen, 2010). This community may indeed represent the “fuzzy” boundary between depression and demoralization, which may partly justify their placement on the same continuum by some authors (Bobevski et al., 2018; Clarke et al., 2002; Guidi et al., 2011).

The community "*loss of purpose*" comprised symptoms related to hopelessness, lack of meaning and existential distress, as well as items related to loss of self-worth, another "core" dimension of demoralization: these dimensions largely contribute to suicidal thinking and may be closely representative of the end stage of the "given-up syndrome", first described by Engel (Tecuta et al., 2015). The community we named "*frustrated isolation*" contained both symptoms related to emotional dysregulation (*irritability-anger*, *lack of emotional control*) and to relationship with self/others (*isolation*, *easily hurt*, *helplessness, feel bad about oneself, guilt*). Emotional dysregulation may result from the sense of poor coping that occurs in demoralization (Robinson et al., 2016b). Some previous factor analyses of the DS have not found these items to co-segregate with items related to interpersonal difficulties (Galiana et al., 2017; Grassi et al., 2017), while refinement of the DS showed their clearer relationship to entrapment and helplessness (Robinson et al., 2016b). Collectively, these symptoms may be indicative of interpersonal sensitivity, a trait-like feature that to leads to the development of pessimism and negative beliefs about the self, and thus may predispose to the development of depression or demoralization (Decety and Batson, 2007; Otani et al., 2018).

These findings may be useful for clinicians. By identifying the main dimensions of depression and demoralization in physically ill subjects, and their connections, we have highlighted symptom groupings that might represent potential clinical subtypes, which the DSM terms "specifiers", and could serve as specific targets for treatment. For instance, it could be interesting to verify if patients displaying predominant loss of purpose would respond differentially to meaning-centered or dignity therapy (Breitbart, 2017; Russo-Netzer et al., 2016), those with frustrated loneliness to cognitive-behavioral or problem solving interventions (Tecuta and Tomba, 2018), those with predominant low morale/mood to mindfulness or emotion-centered interventions (Zimmermann et al., 2018) and those with predominant neurovegetative symptoms or anhedonia to specific pharmacological or non-pharmacological treatments (Belvederi Murri et al., 2018b; Cao et al., 2019; Lee et al., 2018; van Straten et al., 2018).

4.1 Strengths and Limitations

The study is strengthened by the use of a robust methodology to examine symptom interactions. Previous factor models of depression in physically ill patients, in fact, yielded unstable factor structures (Cosco et al., 2012; Dong et al., 2014), possibly because they relied on the assumption of local independence of symptoms or did not account for topological overlap (Contreras et al., 2019). In contrast, the present model is parsimonious examining two conditions with a high degree of overlap (Fried, 2015). However, results need to be interpreted in light of the study methodology, particularly in relation to the choice of assessment instruments. First, demoralization has multiple, albeit similar, conceptual definitions corresponding to different assessment instruments (Tecuta et al., 2015). In particular, this study is based on the DS, which is based on self-report. Although instruments may be largely concordant (Nanni et al., 2018b), the DS displays a lower divergent validity towards depression compared with other instruments, such as the DCPR interview (Tecuta et al., 2015). Similarly, the PHQ is one of the few self-report scales assessing somatic symptoms of depression, but does only contain DSM-defined depressive symptoms out of a wider set (Fried, 2017).

The different number of items of the DS and the PHQ is unlikely to have biased the patterns of connections between symptoms, since the network relies on a rigorous examination of their potential overlap. Nonetheless, future studies investigating this issue may attempt to replicate these results using more detailed measures for sleep disturbance and anhedonia, using clinician-based ratings or employing other methods, such as latent network models (Epskamp et al., 2017). Second, the study has a cross-sectional design, thus the directionality of the edges cannot be determined. Similarly, caution is needed when arguing for a more important causal role of central symptoms in cross-sectional networks, especially that they may be preferential targets for treatment (Bringmann et al., 2019).

. Third, the sample size was relatively small and comprised a relatively old population. Thus, results need to be replicated in larger samples, especially those related to items with lower community replication, and may be less generalizable among younger adults. Fourth, the sample was drawn from various wards of a general hospital, with patients suffering from a range of different physical diseases and we lack detailed information on treatment; future studies should investigate these issues among homogeneous samples, such as diabetes or cardiovascular disease (Belvederi Murri et al., 2017), and investigate the role of medications.

4.2 Conclusions

In conclusion, demoralization and depression are connected but should be considered distinct conditions among physically ill individuals. The identification of specific groupings of symptoms may aid the differential diagnosis between these conditions and may have possible implications for their management.

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Statement of Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Figure Legends

Figure 1. The network represents the relationships between demoralization (DS scale) and depressive symptoms (PHQ-9 scale). In the diagram, symptoms (nodes) with stronger connections are coloured to show their community membership. Lines between symptoms (edges) are colored in green when they represent positive correlations and in red when they represent negative correlations. The edge thickness is proportional to the strength of the association between symptoms. Nodes report abbreviated captions. Nodes corresponding to items 1, 5, 6, 17 and 19 of the DS were reverse-scored and report a modified caption for clarity.

Figure 2. Likelihood plot reporting the probability of each symptom belonging to a community identified by Exploratory Graph Analysis

Table 1. Sample characteristics

Sociodemographic and clinical characteristics		DS, prevalence of most severe rating [a]	%
Age, mean (SD)	62.3 (17.8)	1. There is no value in what I can offer others [b]	7.6
Aged 65 or older, %	54.3	2. My life seems to be pointless	4.3
Gender, F, %	56.5	3. There is no purpose to the activities in my life	5.6
Education, elementary or lower, %	41.6	4. My role in life has been lost	9.4
Employed, %	24.9	5. I no longer feel emotionally in control	3.4
		6. I am in bad spirits [b]	11.4
Depression lifetime, %	19.2	7. No one can help me	5.8
Ongoing prescription of psychotropics, %	37.5	8. I feel that I cannot help myself	12.3
DS total score, mean (SD)	38.5 (20.7)	9. I feel hopeless	8.3
Current demoralization (DS ≥30), %	46.5	10. I feel guilty	4.3
PHQ-9 total score, mean (SD)	9.09 (6.94)	11. I feel irritable	4.3
Current Major Depression (PHQ-9 criteria), %	40.7	12. I cope poorly with life [b]	4.9
		13. I have a lot of regret about my life	6.0
PHQ-9, prevalence of most severe rating [a]	%	14. Life is no longer worth living	3.6
1. Lack of interest or pleasure	19.0	15. I tend to feel hurt easily	7.2
2. Low mood	22.4	16. I am angry about a lot of things	7.2
3. Sleep problems	21.5	17. I am not proud of my accomplishments [b]	2.9
4. Tiredness	36.9	18. I feel distressed about what is happening to me	21.9
5. Appetite problems	18.8	19. I am not a worthwhile person [b]	1.8
6. Feel bad about yourself or that you are a failure or have let yourself or your family down	9.4	20. I would rather not be alive	3.4
7. Lack of concentration	9.2	21. I feel sad and miserable	10.5
8. Slowing or agitation	3.6	22. I feel discouraged about life	13.0
9. Thoughts that you would be better off dead or of hurting yourself in some way	4.0	23. I feel quite isolated or alone	8.1
		24. I feel trapped by what is happening to me	19.5

a. For the PHQ-9, the table reports the percentage of subjects endorsing “3” (“Nearly every day”) as response. For the DS, the table reports the percentage of subjects endorsing “4” (“All the time”) as response.

b. Reverse-scored items: the phrasing has been reversed in the table and subsequent figures for clarity

Figure 1. Network structure and communities of demoralization and depressive symptoms

Table 2. Item replication in the bootstrap procedure

Community name	Items/latent factors	Node labels	Frequency of item replication in the bootstrap iterations				
			1	**2**	**3**	**4**	**5**
Neurovegetative depression	**PHQ1**	PHQ_Appet_prob	**0.9254**	0.0003	0.0053	0.0258	0.0410
	PHQ3	PHQ_Concentrat	**0.9008**	0.0001	0.0038		0.0854
	PHQ4	PHQ_Slow_agit	**0.9004**	0.0001	0.0042		0.0854
	PHQ5	PHQ_Tiredness	**0.861**	0.0007	0.0131	0.0784	0.0420
	PHQ7	PHQ_Int_pleasure	**0.6617**	0.0131	0.0702	0.1767	0.0721
	PHQ8	PHQ_Sleep_prob	**0.5744**	0.0115	0.2922	0.0666	0.0510
Loss of purpose	**latent factor**	lack_purpose		**0.9977**	0.0009	0.0001	0.0012
	latent factor	death_ideation		**0.9973**	0.0006	0.001	0.001
	DS2	Life_pointless		**0.9958**	0.0021	0.0005	0.0014
	latent factor	lack_value	0.0028	**0.9652**	0.0024	0.0175	0.0104
	DS9	Hopelessness	0.0004	**0.8578**	0.0017	0.1354	0.004
	DS12	Inab_Coping_R	0.0016	**0.7950**	0.0120	0.1692	0.0197
	DS8	Cant_help_self	0.0065	**0.5405**	0.0500	0.3698	0.0314
Frustrated isolation	**latent factor**	guilt_pride	0.0004	0.0016	**0.9956**	0.0003	0.0020
	latent factor	irritab_anger	0.0015	0.0006	**0.9919**	0.0018	0.0040
	DS7	Helplessness	0.0001	0.0077	**0.9874**	0.0011	0.0034
	DS15	Easily_hurt	0.0134	0.0007	**0.9684**	0.0049	0.0119
	DS21	Isolation	0.0083	0.0192	**0.9403**	0.0151	0.0152
	DS5	Lack_emot_contr	0.0044	0.0120	**0.9375**	0.0346	0.0111
	PHQ6	PHQ_Bad_self	0.0097	0.0154	**0.8848**	0.0624	0.0260
Low mood/morale	**DS18**	Distress	0.0118	0.0713	0.0121	**0.9048**	
	DS24	Entrapment	0.012	0.0710	0.0122	**0.9048**	
	latent factor	mood_discourag	0.0111	0.1318	0.0236	**0.8238**	0.0086

Latent factors result from the combination of items with high topological overlap.

Figure 2. Likelihood plot reporting the probability of each symptom belonging to a community identified by Exploratory Graph Analysis

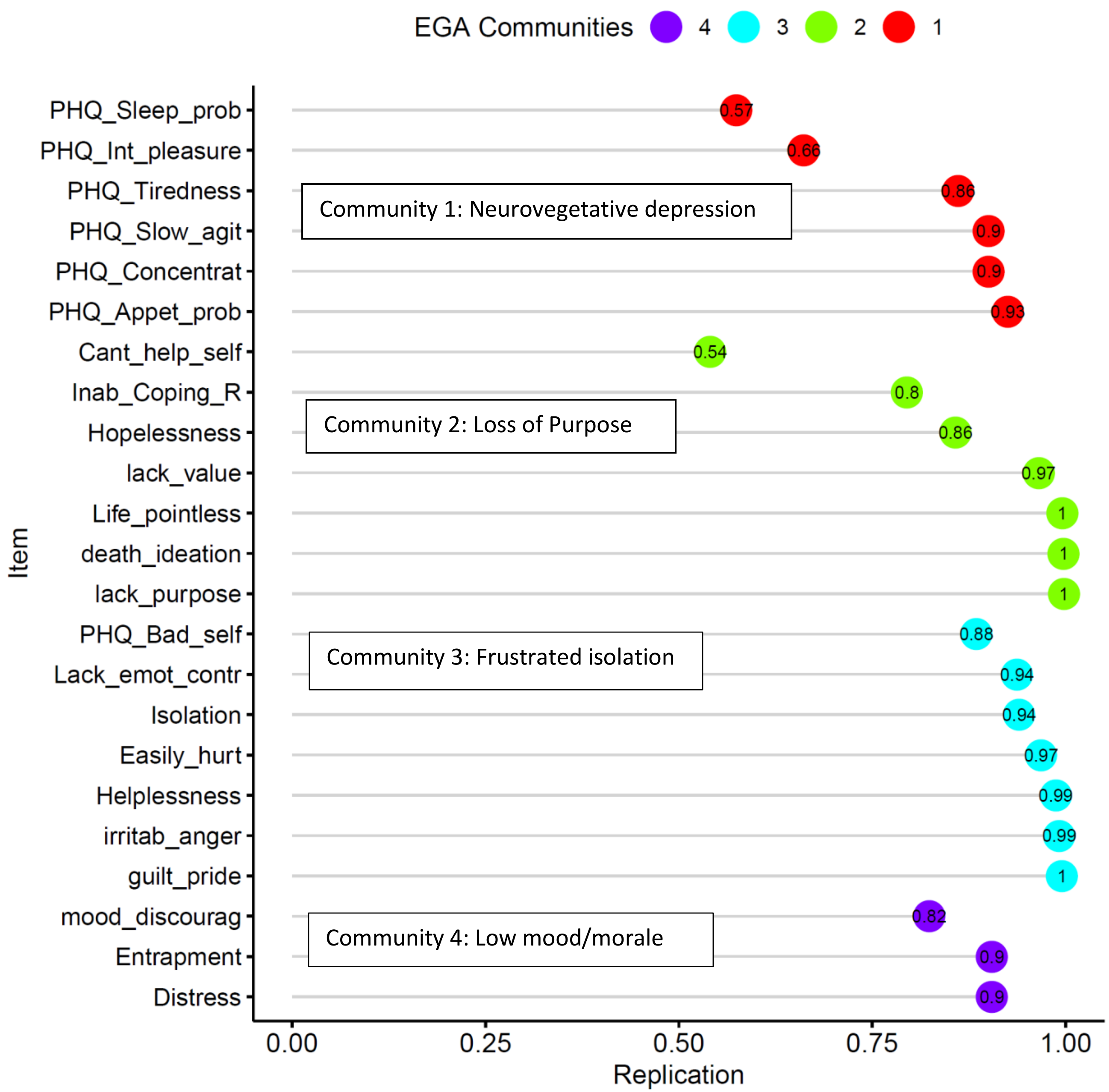


Table S1. Aggregation of items with high topological overlap

Groups of items detected as redundant		Labels	Combined items	Latent factors	Labels
1)	**DS21**	**Sadness**	**Sadness**	**Low mood/ discouragement**	mood_discourag
	DS22	**Discouragement**	**Discouragement**		
	PHQ2	**PHQ_Low_mood**	**PHQ_Low_mood**		
	DS6	**Low_spirit_R**	**Low_spirit_R**		
2)	**DS10**	**Guilt**	**Guilt**	**guilt/lack of pride**	guilt_pride
	DS13	**Regret**	**Regret**		
	DS17	**Lack_pride_R**	**Lack_pride_R**		
3)	**DS3**	**Lack_purp_activ**	**Lack_purp_activ**	**lack of purpose**	lack_purpose
	DS4	**Lack_purp_role**	**Lack_purp_role**		
	DS2	*Life_pointless*	*Not combined*		
4)	**DS14**	**Lack_worth_living**	**Lack_worth_living**	**death ideation**	death_ideation
	DS20	**Rather_dead**	**Rather_dead**		
	PHQ9	**PHQ_Death_wish**	**PHQ_Death_wish**		
5)	**DS19**	**Not_worthwhile_R**	**Not_worthwhile_R**	**lack of value**	lack_value
	DS1	**No_Value_R**	**No_Value_R**		
6)	PHQ4	*PHQ_Tiredness*	*Not combined*		
	PHQ5	*PHQ_Appet_prob*	*Not combined*		
	PHQ1	*PHQ_Int_pleasure*	*Not combined*		
7)	DS2	*Life_pointless*	*Not combined*		
	DS4	*Lack_purp_role*	*Not combined*		
8)	DS6	*Low_spirit_*	*Not combined*		
	DS12	*Inab_Coping_R*	*Not combined*		
9)	**DS11**	**Irritability**	**Irritability**	**irritability/anger**	irritab_anger
	DS16	**Anger**	**Anger**		
10)	DS18	*Distress*	*Not combined*		
	DS24	*Entrapment*	*Not combined*		
11)	PHQ7	*PHQ_Concentrat*	*Not combined*		
	PHQ8	*PHQ_Slow_agit*	*Not combined*		

Combination of DS and PHQ-9 items with high topological overlap: items displaying high topological overlap (in bold) were combined into their corresponding latent factor, unless they were judged as conceptually distinct (in italic).

Table S2. Edge weights in the network, where the edge weight reflects the strength of connection between symptoms

community		Life_pointless	lack_purpose	Lack_emot_contr	Helplessness	Cant_help_self	Hopelessness	guilt_pride	irritab_anger	Inab_Coping_R	death_ideation	Easily_hurt	Distress	lack_value	mood_discourag	Isolation	Entrapment	PHQ_Int_pleasure	PHQ_Sleep_prob	PHQ_Tiredness	PHQ_Appet_prob	PHQ_Bad_self	PHQ_Concentrat	PHQ_Slow_agit
	community	*2*	*2*	*3*	*3*	*2*	*2*	*3*	*3*	*2*	*2*	*3*	*4*	*2*	*4*	*3*	*4*	*1*	*1*	*1*	*1*	*3*	*1*	*1*
2	**Life_pointless**		0.39	0.01	0.15		0.21			0.07	0.07			0.12		0.16	0.01	0.07	0.02			0.12		
2	**lack_purpose**	0.39				0.08	0.05			0.01	0.18			0.06	0.04	0.02								
3	**Lack_emot_contr**	0.01			0.15	0.10		0.03	0.05			0.10			0.09	0.01	0.04		0.03			0.03		0.03
3	**Helplessness**	0.15		0.15				0.05	0.12			0.08				0.21								
2	**Cant_help_self**		0.08	0.10			0.10			0.11			0.06	0.03			0.08	0.02				0.06	0.02	
2	**Hopelessness**	0.21	0.05			0.10				0.11	0.24		0.10		0.15		0.08	0.04						
3	**guilt_pride**			0.03	0.05				0.11							0.15						0.15		
3	**irritab_anger**			0.05	0.12			0.11			0.01	0.20			0.04		0.03		0.02			0.16		0.02
2	**Inab_Coping_R**	0.07	0.01			0.11	0.11						0.01	0.20	0.10			0.03				0.10		
2	**death_ideation**	0.07	0.18				0.24		0.01					0.10	0.04									
3	**Easily_hurt**			0.10	0.08				0.20									0.05		0.06		0.04		
4	**Distress**					0.06	0.10			0.01					0.17		0.41			0.03		0.02		
2	**lack_value**	0.12	0.06			0.03				0.20	0.10							0.02			-0.02		0.02	
4	**mood_discourag**		0.04	0.09			0.15		0.04	0.10	0.04		0.17			0.12	0.19	0.13	0.01	0.02	0.01	0.06		
3	**Isolation**	0.16	0.02	0.01	0.21			0.15							0.12				0.02			0.02	0.05	0.06
4	**Entrapment**	0.01		0.04		0.08	0.08		0.03				0.41		0.19			0.01		0.08		0.03	0.02	
1	**PHQ_Int_pleasure**	0.07				0.02	0.04			0.03		0.05		0.02	0.13		0.01		0.03	0.27		0.10	0.06	0.04
1	**PHQ_Sleep_prob**	0.02		0.03					0.02						0.01	0.02		0.03		0.01	0.06	0.04	0.03	0.02
1	**PHQ_Tiredness**											0.06	0.03		0.02		0.08	0.27	0.01		0.21		0.06	
1	**PHQ_Appet_prob**													-0.02	0.01				0.06	0.21			0.13	0.06
3	**PHQ_Bad_self**	0.12		0.03		0.06		0.15	0.16	0.10		0.04	0.02		0.06	0.02	0.03	0.10	0.04				0.03	
1	**PHQ_Concentrat**					0.02								0.02		0.05	0.02	0.06	0.03	0.06	0.13	0.03		0.44
1	**PHQ_Slow_agit**			0.03					0.02							0.06		0.04	0.02		0.06		0.44	

For ease of reading, zeroes are not reported and stronger edges are highlighted in darker green.

Figure S1. Strength centrality of symptoms

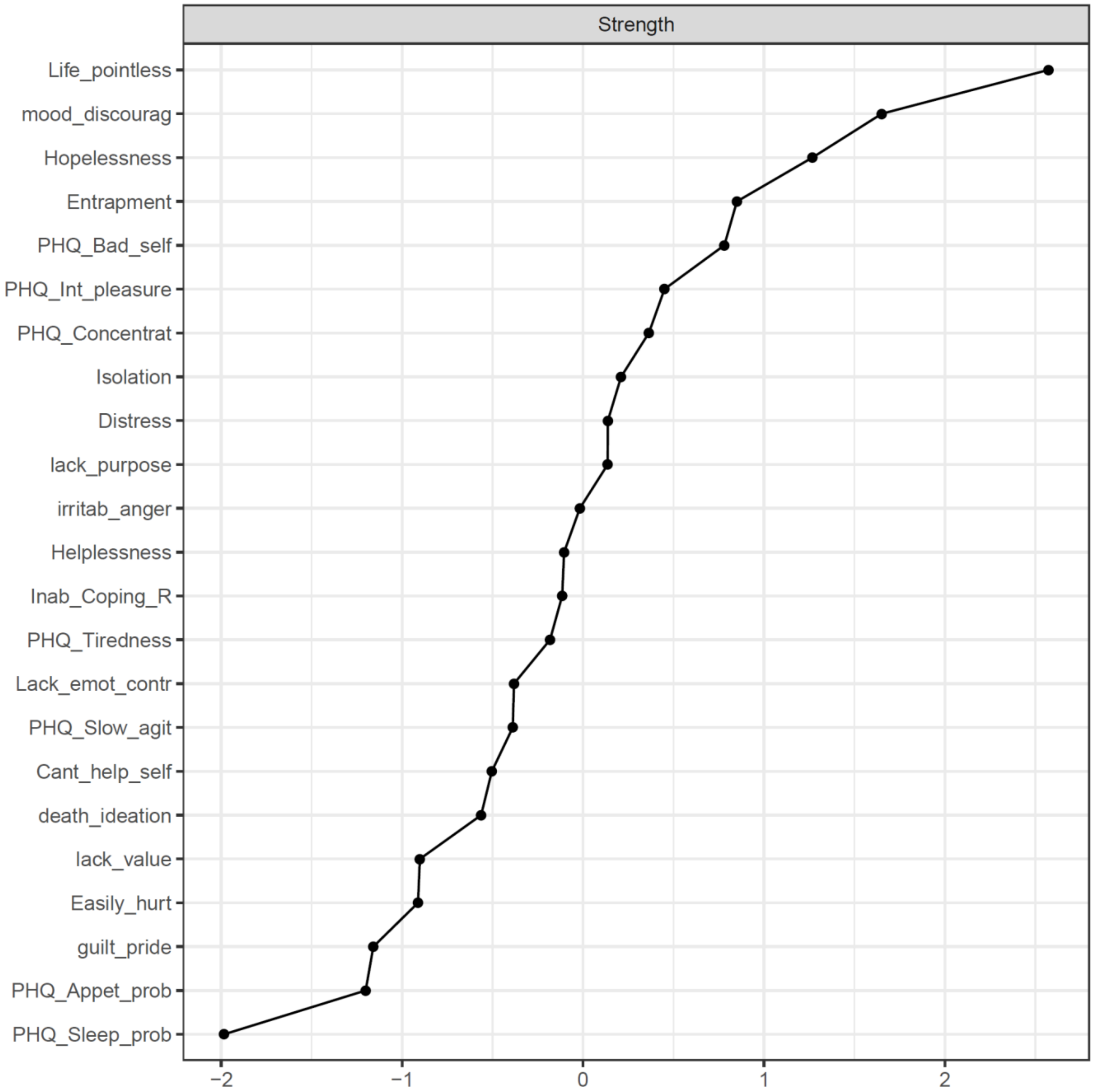


Table S3. Communities of symptoms and network loadings

	1	2	3	4
Neurovegetative depression				
PHQ_Int_pleasure	0.208			
PHQ_Sleep_prob				
PHQ_Tiredness	0.275			
PHQ_Appet_prob	0.226			
PHQ_Concentrat	0.360			
PHQ_Slow_agit	0.285			
Loss of purpose				
Life_pointless		0.353	0.196	
lack_purpose		0.311		
Cant_help_self		0.130		
Hopelessness		0.291		0.191
Inab_Coping_R		0.204		
death_ideation		0.242		
lack_value		0.209		
Frustrated isolation				
Lack_emot_contr			0.168	
Helplessness			0.265	
guilt_pride			0.220	
irritab_anger			0.288	
Easily_hurt			0.193	
Isolation			0.175	
PHQ_Bad_self		0.115	0.177	
Low mood/morale				
Distress				0.340
mood_discourag		0.135	0.140	0.212
Entrapment				0.354

Figure S2. Stability of node strength in the case-dropping procedure

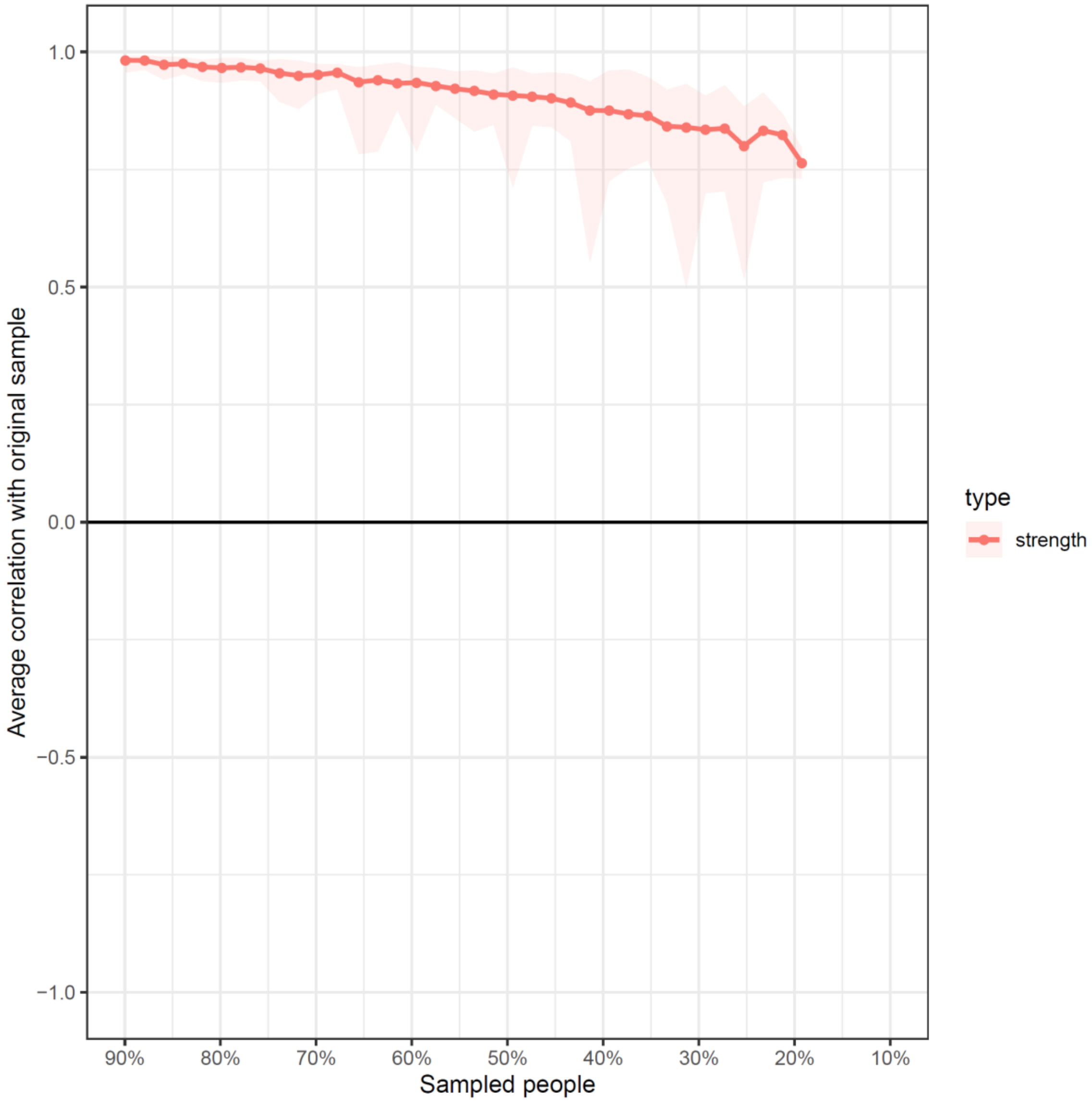
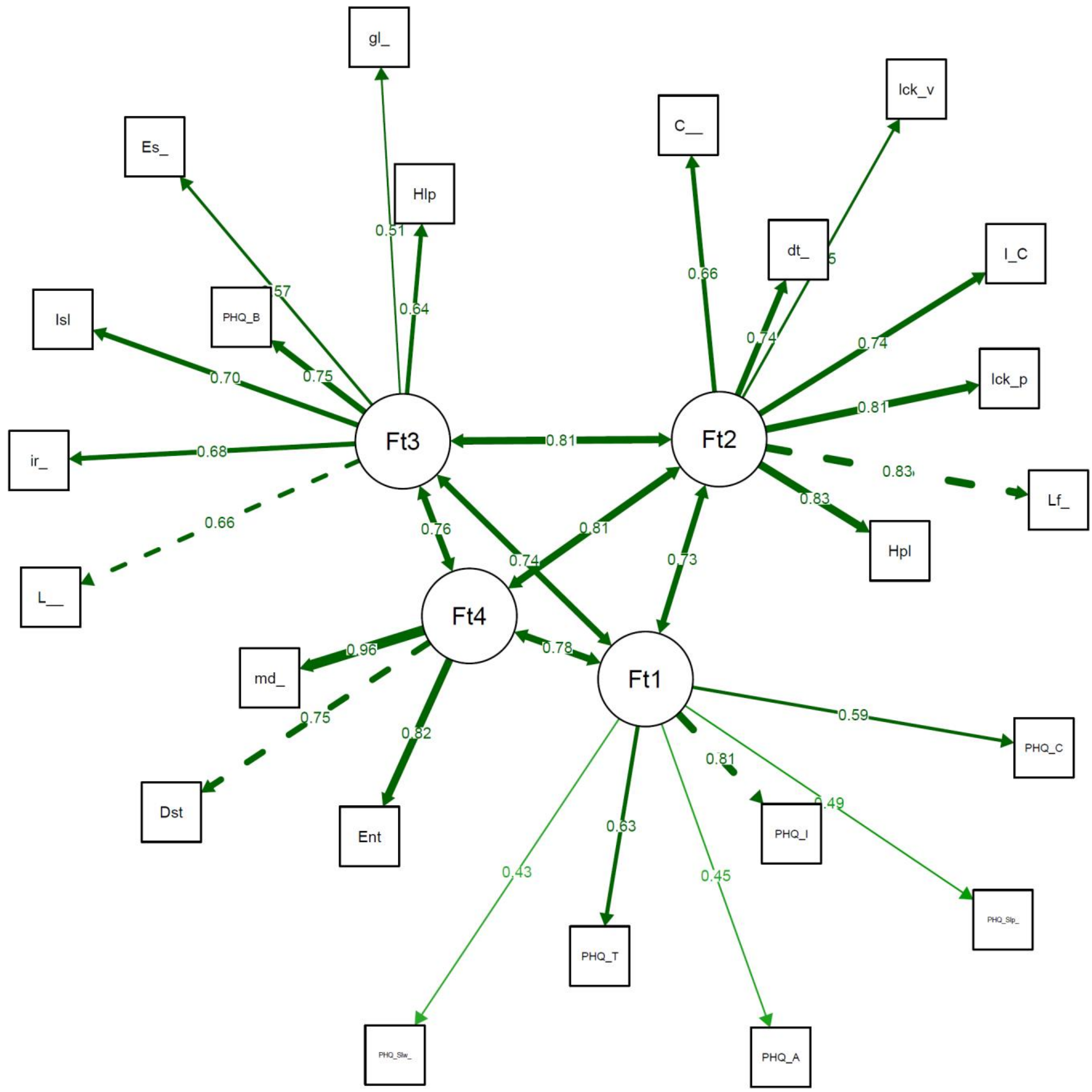


Figure S3. EGA model converted into a latent variable model



In order to compare the results of Exploratory Graph Analysis (EGA) with those obtained from Exploratory Factor Analysis (EFA), the EGA structure was converted into the equivalent latent factor model and evaluated using Confirmatory Factor Analysis. Here, items belonging to each community (see Table 2 for item groupings) load onto distinct factors (Ft1 to Ft4 in the figure).

Table S4. Results of Exploratory Factor Analysis

	ML1	ML2	ML4	ML3	
Life pointless	**0.8**	0.21	0.35	0.14	similar to community 2
lack of purpose	**0.77**	0.26	0.28	0.13	
Death ideation	**0.64**	0.25	0.28	0.19	
Hopelessness	**0.6**	0.44	0.26	0.19	
Lack of value	**0.55**	0.15	0.11	0.17	
Inability Coping R	**0.47**	0.36	0.29	0.22	
Distress	0.28	**0.78**	0.16	0.11	similar to community 4
Entrapment	0.28	**0.72**	0.27	0.2	
Mood discouragement	0.4	**0.64**	0.38	0.27	
PHQ Tiredness	0.16	**0.43**	0.18	0.36	
PHQ Interest pleasure	0.33	**0.41**	0.29	0.36	
Can't help self	0.39	**0.40**	0.22	0.17	
irritability anger	0.14	0.29	**0.63**	0.2	Identical to community 3
Guilt pride	0.17	0.06	**0.59**	0.12	
Helplessness	0.36	0.1	**0.57**	0.11	
Easily hurt	0.14	0.26	**0.51**	0.1	
PHQ Bad self	0.34	0.29	**0.5**	0.22	
Isolation	0.43	0.13	**0.49**	0.25	
Lack emotional control	0.27	0.29	**0.46**	0.16	
PHQ Concentration	0.24	0.16	0.11	**0.7**	similar to community 1
PHQ Slow agitation	0.14	0.05	0.14	**0.62**	
PHQ Appetite problems	0.04	0.26	0.16	**0.42**	
PHQ Sleep problems	0.18	0.19	0.25	**0.26**	
SS loadings	3.83	3.06	3.01	1.92	
Proportion variance.	0.17	0.13	0.13	0.08	
Cumulative variance.	0.17	0.3	0.43	0.51	

Results from Exploratory Factor Analysis after determination of the number of factors with parallel analysis (n=4). The items in red did not belong to the same community of other items in the corresponding EGA analysis.

Table S5. Comparison between exploratory graph analysis and exploratory factor analysis

Fit index	The Entropy Fit Index	Total correlation of the dataset	Average entropy of the dataset
EGA model (4 communities)	-13.15794	-9.820804	-32.79955
EFA model (4 factors)	-13.55481	-9.594019	-32.74285