A body-mind map

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DOI:
10.33612/diss.116932931

General discussion

Partly based on: Bekhuis E, Olde Hartman TC, Boschloo L, Lucassen PLBJ.
A novel approach to psychopathology: the example of depression.

Br J Gen Pract 2019;69:146-7.

The aim of this thesis was to get a deeper understanding of the co-occurrence of depressive, anxiety and somatic symptoms. The first part focused on epidemiological aspects of this co-occurrence, while the second part examined its clinical aspects in consultations and interventions. In this chapter, we draw up the balance. What do the results tell us about the map of body and mind? Which insights do we get into the association between depressive, anxiety and somatic symptoms, its underlying mechanisms and its specificity? Which implications do these findings have from a clinical and scientific perspective?

Findings in perspective

The association between depressive, anxiety and somatic symptoms

We showed that depressive and anxiety symptoms and somatic symptoms frequently co-occur. The prevalence of somatic symptom clusters was two to four times higher in patients with a depressive or anxiety disorder compared to persons without a depressive or anxiety disorder (Chapter 2). This association was apparent for both cognitive/affective and neurovegetative depressive and anxiety symptoms (Chapter 5). Furthermore, the co-occurrence has a negative effect on prognosis. We found that persons with multiple somatic symptom clusters had a two times higher risk of persistence of a major depressive disorder than patients without somatic symptoms (Chapter 4). It is therefore not surprising that the co-occurrence was an important subject of conversation between patients and physicians in primary care consultations (Chapter 8). The strength and consistency of the relation between depressive, anxiety and somatic symptoms underline that it is crucial for prevention and treatment programs to take into account all types of symptoms in order to improve patients' outcomes.

Our findings do not only indicate that the association between depressive, anxiety and somatic symptoms has negative consequences; they also showed that it could comprise an important treatment opportunity. That is, as depressive and anxiety symptoms improved during an intervention, somatic symptoms improved simultaneously (Chapter 10 and 11). We suggested that some of these improvements in somatic symptoms could be mediated by direct treatment effects on depressive or anxiety symptoms. For instance, the somatic symptom low in energy responded indirectly to the addition of pharmacotherapy to psychotherapy, and part of this effect may have been mediated by direct treatment effects on the depressive symptoms feeling entrapped or emotional lability (Chapter 10). On the other hand, we found that antidepressants indirectly effectuated a greater improvement in depressed mood than cognitive behavioral therapy, which may partly have been mediated by improvements in general somatic symptoms (Chapter 11). Targeting depressive and anxiety symptoms in patients with somatic

symptoms or vice versa could therefore be an effective strategy in the treatment of patients with both symptom dimensions. In primary care consultations, patients and GPs also took advantage of this simultaneous improvement by creating symptom management strategies aimed at negative emotions in order to improve somatic symptoms (Chapter 8 and 9).

Underlying mechanisms

To improve the outcome of patients with co-occurring depressive, anxiety and somatic symptoms, it is crucial to unravel the mechanisms leading to this association. Therefore, this thesis explored three mechanisms that have been suggested to explain their co-occurrence: 1) the symptom types are expressions of the same underlying construct, 2) they directly influence each other, and 3) they have shared risk factors. The first hypothesis that depressive, anxiety and somatic symptoms reflect one underlying construct was acknowledged by some patients in consultations for persistent physical symptoms, who described these symptoms as an integrated whole with depressive and anxiety symptoms (Chapter 8). Our empirical findings, however, provided conflicting evidence for this theory. The hypothesis was supported by that specific symptoms of the depressive, anxiety as well as somatic domain responded in a similar way to interventions (Chapter 10 and 11). In addition, we examined the co-development of depressive and anxiety versus functional somatic symptoms during adolescence, as it has been suggested that functional symptoms are expressions of depressive and anxiety symptoms in children [50]. Indeed, we found patterns of symptom development that could be in line with the theory that children learn to interpret and express the signals as affective rather than somatic symptoms while they mature (Chapter 2). As we were not able to study this underlying mechanism directly, however, our findings form a basis for further research.

In contrast to findings that might suggest a common underlying construct, we found that depressive and anxiety symptoms more strongly clustered with each other than with somatic symptoms (Chapter 2 and 5). Some patients with persistent physical symptoms also recognized this distinction between the symptoms as they firmly rejected that their somatic symptoms were part of an affective disorder in consultations (Chapter 8). Still, we found that the clusters of depressive/anxiety and somatic symptoms were strongly related (Chapter 2 and 5). This is in accordance with research in a large primary care sample [406], which demonstrated that the best fitting factor structure of these symptoms consisted of a general factor incorporating shared variance between the symptom domains, but also separate factors for depressive, anxiety as well as somatic symptoms incorporating their unique variance [406]. Our studies took a more detailed look, and demonstrated further heterogeneity within clusters of depressive/anxiety and

somatic symptoms as individual symptoms showed unique patterns of co-occurrence and responses to treatment (Chapter 5, 6, 10, 11). These findings indicate that although depressive, anxiety and somatic symptoms may have a common basis that accounts for some of their variance, they also have their own specific characteristics. These common as well as specific characteristics are captured in a hybrid model [407,408].

Our findings provided some evidence for the second mechanism: depressive, anxiety and somatic symptoms directly influence each other [51,178]. This theory was recognized by patients with persistent physical symptoms, who frequently described them in primary care consultations (Chapter 8). They described relations with unidirectional as well as bidirectional causal interferences and referred to vicious circles in which somatic symptoms and emotions kept worsening each other. We first examined this theory empirically by studying if somatic symptoms could influence depressive symptoms. We studied if specific clusters of somatic symptoms predicted the two-year prognosis of major depressive disorder (Chapter 4). We found significant predictive effects for cardiopulmonary, gastrointestinal and general symptoms. This association did not change substantially after adjusting for covariates (e.g., psychiatric characteristics, somatic diseases, lifestyle factors and disability; except for a small change after adjusting for the severity of baseline depressive symptoms), suggesting that the somatic symptom clusters had a direct negative impact on the depressive disorder. This association was specific for somatic symptom clusters that were chronic and occurred in combination with other clusters (Chapter 4). This might indicate a dose-response effect, which could be in line with the theory that symptoms directly influence each other.

Furthermore, we found that psychosocial reasons for encounter in primary care weakly predicted if a subsequent health problem constituted FSS (Chapter 7). This might indicate that the psychosocial problems caused functional somatic symptoms at a later moment in time. Interestingly, this association was not apparent in frequent attenders. This probably reflects the complex organization of consultation patterns, which is known to be influenced by a considerable number of interacting factors [311-313].

Other indirect support for the theory that symptoms directly impact on each other is provided by our finding that somatic symptoms may respond indirectly to an intervention, mediated by direct effects of this intervention on depressive and anxiety symptoms, and vice versa (Chapter 10 and 11). Interestingly, we found that the core depressive symptom depressed mood responded better to the addition of antidepressants to psychotherapy compared to psychotherapy alone (Chapter 10) and SSRIs compared cognitive behavioral therapy (Chapter 11). These responses seemed not to be direct, but indirect via improvements in other symptoms, which could include anxiety or somatic symptoms. This indicates that depressed mood may respond to these interventions because it is causally related with anxiety and somatic symptoms. These findings

highlight the importance of considering such causal trans-dimensional relations to understand the effects of interventions on core psychiatric symptoms. As we examined the responses of symptoms during the same time period, however, conclusions about the temporal ordering of indirect treatment effects are precluded. Still, a recent longitudinal study corroborated that somatic symptoms can mediate treatment effects of cognitive behavioral therapy for insomnia on depressive symptoms [409]. In order to gain more insight into the influence of causal relations among symptoms on their responses to an intervention, more longitudinal research with larger samples is warranted.

Finally, we investigated the third mechanism: depressive, anxiety and somatic symptoms share risk factors [51,222,410]. We investigated a number of suggested risk factors (including sociodemographic characteristics, psychiatric and somatic comorbidity, lifestyle, life events, parenting style) and found that none of them explained the co-occurrence (Chapters 2-4). Previous prospective studies have indicated that the magnitude of the effects of these factors on depressive, anxiety and somatic symptoms is very small, even though the effects were significant [51,106,107,114,178,228]. Therefore, these external factors on their own probably do not have an important role in explaining the co-occurrence.

Specificity of associations

It has repeatedly been argued that the complexity of the organization of symptoms does not match the rigid definitions of disorders in classification systems [411,412]. This realization has supported changes towards a more dimensional classification [411,412]. The DSM-5 has for instance abandoned the classification of somatic symptoms based on their organ system in somatic symptom disorder, included an anxiety specifier for depressive disorder, and introduced cross-cutting symptom dimensions regardless of the primary disorder [16,413]. Our findings support such a dimensional approach instead of a disorder-focused approach as we showed that all symptoms have common characteristics that lead to clustering on varying hierarchical levels between which boundaries are fuzzy [232,265,378,406]. For instance, we found that depressive/anxiety and somatic symptoms formed two dimensions (Chapter 2 and 5), which were strongly related. Similarly, although all somatic symptoms were connected within the somatic dimension, subdimensions formed based on body systems that did not match the categories of chronic fatigue syndrome, fibromyalgia syndrome and irritable bowel syndrome (Chapter 5 and 6). The body system subdimensions had both differential and similar characteristics. All somatic subdimensions showed for example comparable cross-sectional associations to depressive and anxiety disorders (Chapter 3), while only three of the four predicted the course of major depressive disorder (Chapter 4).

Our results also underline that symptom domains are heterogeneous [69,80,93]. This heterogeneity was apparent for patterns of co-occurrence and response to treatment. For instance, although anxiety and guilt were both part of the cognitive/affective subdimension, anxiety showed a ten times stronger association with the somatic dimension than guilt (Chapter 5). Furthermore, antidepressants were more effective for the depressive symptoms depressed mood and guilt but not thoughts of suicide than cognitive behavioral therapy (Chapter 11). That individual symptoms within the same symptom domain show differential responses to treatment, even in opposite directions, has also been indicated by other work [91,409]. This is not surprising given that some somatic symptoms are well-known side effects of psychopharmaceutic agents [414]. Still, it underlines that clinically highly important characteristics of specific symptoms can be concealed when they are combined into a sum score [69,378].

A dimensional classification favors symptom or syndrome labels over diagnostic labels. Interestingly, we showed that most patients used this approach in consultations for persistent physical symptoms by referring to their complaints as “fatigue” or “worry” instead of “chronic fatigue syndrome” or “anxiety disorder” (Chapter 8). Labels for affective disorders that were introduced by physicians could be rejected firmly by patients. Nevertheless, other patients openly spoke about their experiences with affective disorders. This inconsistency probably reflects the different ways in which patients view such labels. Some patients have reported that they feel that labels for psychiatric disorders are helpful to remove blame from themselves and indicate that treatment options are available [415]. Other patients, however, feel that these labels are stigmatizing as they insinuate mind-body dualism and are too simplistic to fully explain their symptoms [321]. Furthermore, it has been highlighted that labels can lead to medicalization of everyday problems, alienate patients from their experience and decrease perceived self-control, and in this way worsen symptoms [61,416]. To avoid such unfavorable effects, it has been argued that physicians should introduce labels for psychiatric disorders with care [61]. Preferably, the patient and physician create a narrative together that captures the symptoms and their underlying mechanisms in the patient’s own words [417]. Still, clinical observations indicate that labels are increasingly incorporated in patients’ narratives. It should be noted, however, that it is unclear if this is a result of the integration of labels in everyday language, or if patients feel that this is the appropriate way to communicate with physicians.

Dueling with dualism in clinical care

Due to the ancient dualistic culture in Western medicine, the care for depressive, anxiety and somatic symptoms has become splintered. This is apparent from the split between psychiatry and somatic disciplines and the tendency of physicians to focus on either field

in the consultation [288,418]. This indicates that patients with co-occurring depressive, anxiety and somatic symptoms can easily be missed and/or undertreated. Our findings therefore stress that physicians from all disciplines should adequately consider this co-occurrence in their assessments and management. Nevertheless, some physicians have reported to find it challenging to bring up the combination of the symptom domains [326,327]. They sometimes unintendedly ignore or block emotional clues of patients with somatic symptoms [343], even though such patients typically seek social support [419]. To enhance integration of the care for these types of symptoms, important steps have been made in health care. Numerous multidisciplinary programs have been developed with encouraging effects on overall health [420-423]. A collaborative care treatment for depressive symptoms in patients with cancer, for example, lowered depressive symptoms, pain and fatigue severity and improved functioning [421]. Furthermore, more insight has been derived into the effects of interventions on symptoms from multiple dimensions (e.g., Chapter 10 and 11), which could help to identify treatment modalities that are most effective for patients with depressive, anxiety as well as somatic symptoms. Finally, training programs are currently being developed for general practitioners, who have a central role in the treatment of patients with depressive, anxiety as well as symptoms [325,362], which strongly focus on communication.

In consultations for patients with depressive, anxiety and somatic symptoms, clinical experts commonly advice patient-centered communication [318,356,362]. This concentrates on staying closely to the experience of the patient, showing empathy and shared decision making [424]. Central is that the patient feels understood and supported and is an equal partner in the consultation [424]. Patients have reported that they highly value such elements of patient-centered care as it gives them the feeling that they are taken seriously [322]. We found that involvement of the patient in the creation of management strategies was the most important characteristic associated with the adoption of symptom management strategies (Chapter 9). Furthermore, it has been shown that patients are much more likely to adopt explanations that are co-created than those that are created entirely by the physician [425]. This is in line with the development of patients' explanatory models we observed if the physician and the patient collaboratively moved towards novel types of explanations (Chapter 8).

Despite that physicians are frequently encouraged to adopt patient-centered communication, it has been demonstrated that some of the recommended pillars for this type of communication are inconsistently used in consultations for depressive, anxiety and somatic symptoms [343,426-431]. Adopting the network approach as an underlying framework may help physicians to adopt a patient-centered communication style. First, the approach encourages physicians to concentrate on symptoms that are relevant to the specific patient, as well as external triggers and causal relations that the patient has

experienced. In addition, symptoms in a network can be ordered according to view of the patient and, therefore, it may come naturally to avoid the use of diagnostic labels or dualism embedded in the medical realm. Third, since a network consists of small building blocks (symptoms) instead of large constructs (disorders), it may be easier to identify targets for treatment that seem manageable. Finally, the network approach advocates low-intensity treatment like symptom management strategies instead of long psychotherapies or medication, as small interventions can have dramatic effects via ongoing feedback loops among symptoms [15].

A potentially valuable tool to incorporate the network approach into clinical care is a data-driven network that can be constructed if a patient monitors symptoms during several weeks with ecological momentary assessment [15,84,432,433,433]. Such a personalized network provides a draft of the way symptoms and external triggers may interact in a specific individual, and can be used as a basis to create a person-specific network that is accordance with the experience of the patient. This person-specific network can be used in treatment to identify potential targets for interventions on three levels: 1) external triggers of symptoms, 2) central symptoms, or 3) connections among symptoms [15]. Trying to eliminate external triggers, for example by solving relational problems that triggered worry, is a good starting point. However, not all external triggers can be removed, and feedback loops among symptoms might continue even after triggers have been eliminated. The next step is to treat specific symptoms, especially if they are central in the network. For example, a short treatment of hot flushes in a depressed postmenopausal woman with hormone replacement therapy might improve insomnia and result in a cascade of improvements in other symptoms (less fatigue, more concentration, and less guilt, worry and sadness). In this context, interventions specifically targeted at individual symptoms such as web-based mini-interventions for worry and insomnia are highly promising [434]. A final treatment option is to target connections in the network, such as feeling guilty over concentration problems. In this instance, cognitive techniques to lessen the tendency of an individual to blame themselves could give symptoms the opportunity to recover and help to build resilience for when symptoms recur. Before data-driven networks can be implemented as a tool in clinical care, however, exploratory research on several fundamental terrains is warranted, including whether the graphs offer more insight into mechanisms underlying symptoms than a regular consultation, and whether they are feasible to use in time-restrained consultations.

By identifying specific targets for treatment, the application of the network approach could also help to identify interventions that are likely to be effective for an individual patient [433]. We found that this “precision medicine” has the potential to increase efficacy of interventions for depressive symptoms (Chapter 11). Furthermore, tailoring symptom management to the patient’s narrative seemed to be an important prerequisite

for the adoption of strategies (Chapter 9). An easily applicable way to personalize treatment in clinical care is to focus on symptom profiles of patients. Our findings indicated for example that SSRIs were more effective in the treatment of patients with specific depressive, anxiety and somatic symptoms (e.g., thoughts of suicide, panic, general somatic symptoms) than cognitive behavioral therapy (Chapter 11). Taking into account such responses of differential (types of) symptoms to interventions could help to balance whether the burden and side effects of an intervention outweigh its potential benefits for a particular person. In this respect, focusing on symptom dimensions such as cognitive/affective, neurovegetative and musculoskeletal symptoms has the advantage of offering parsimonious information that can easily be converted to clinical practice. However, individual symptoms capture a higher level of heterogeneity and, because they have varying levels of clinical urgency, could help to predict the benefits of an intervention for a person more specifically. For example, suicidality is of higher importance to target with an intervention than concentration problems, while the latter is more urgent when a patient's job requires a high concentration level than when the job does not.

Methodological considerations

For the interpretation of the results of this thesis, several methodological aspects should be taken into account. Although we have discussed various issues in detail in the corresponding chapters, we would like to highlight some considerations that need further reflection.

This thesis made use of several databases that were restricted to specific situations and populations. Examples include the extended set of consultations with specially trained GPs and patients with multiple persistent physical symptoms (Chapter 8 and 9) and the sample of patients with a mild to moderate depressive disorder (Chapter 10). A limitation of this focus is that it reduces the generalizability of the results to, for instance, regular primary care consultations with patients with persistent physical symptoms (Chapter 8 and 9) and all patients with a depressive disorder (Chapter 10). This underlines the strength of the population based databases that were used for others studies in this thesis (Chapter 2 and 6). Furthermore, most databases focused on patients with one primary type of symptoms, such as persistent physical symptoms or a depressive disorder. Although patients with one of these types of symptoms often also report other types of symptoms addressed in this thesis, it is important to keep in mind these studies did not focus explicitly on patients who reported the combination of depressive, anxiety and/or somatic symptoms. An exception is the NESDA database (Chapter 3, 4 and 5) [172], which included patients with depressive as well as anxiety disorders. To increase insight into the population of patients with the co-occurrence of depressive, anxiety and somatic symptoms, more studies with a transdiagnostic inclusion process are warranted.

Another limitation includes that it was difficult to differentiate between somatic symptoms sufficiently and insufficiently explained by somatic or psychiatric disorders. To determine which somatic symptoms were functional, we used self-report questionnaires (e.g. Chapter 2) as well as diagnostic codes registered by GPs in electronic records (e.g. Chapter 7). Even though a clinical assessment by a GP may more reliably indicate if a symptom is or is not sufficiently explained by diseases than the answer of a patient to a brief question without further explanation about these symptoms, both methods are not fully reliable. This problem reflects the difficulty in clinical practice to establish if a symptom is sufficiently explained by somatic or psychiatric diseases. As the presentation of diseases strongly differs across patients (take for instance the poor correlation between abnormalities on MRIs and experienced pain in patient with a spinal disc herniation) [30], it is difficult to determine if a symptom is more severe or persistent than can be expected based on a particular disease. Furthermore, due to varying opinions across clinicians about with which level of certainty a symptom can be classified as functional [30], it is challenging to formulate one uniform definition of functional somatic symptoms. Several important classification systems have shifted their focus to the presence of multiple and/or persistent somatic symptoms that are disturbing for the patient, independent of whether these symptoms are explained or unexplained by disorders [16, 43]. This approach of neglecting the presence of underlying diseases but focusing on what is observed (i.e., the symptom), which was adopted in several studies of this thesis (Chapters 3, 4, 5, 6, 8, 9, 10 and 11), is highly promising to increase uniformity in research and clinical practice.

Several chapters of this thesis concentrated on the differential characteristics of individual depressive, anxiety and/or somatic symptoms. This focus increased insight into symptom-specific characteristics, but it increased also the number of conducted tests and, therefore, the risk of type I errors [435]. We used regularization in network models to lower this risk [398]. However, it has been questioned whether this method is strict enough, especially in the study of treatment effects [436,437]. We did not use stricter corrections for multiple testing because of the exploratory nature of our research questions. Therefore, it is important to keep in mind that hypothesis-testing studies are needed to confirm some hypotheses that have been generated by our studies.

A final consideration is related to our use of individual items of rating scales to measure specific symptoms. As these scales have been designed for analyses with scale scores, they have several limitations in the analysis of individual symptoms. First, the inter-rater reliability of single items has been questioned [69,437,438]. Second, as some scales measure only the frequency of symptoms (e.g., the Four-Dimensional Symptom Questionnaire [174]), the items' clinical relevance in terms of associated distress and functional impairment remains unclear. The absence of cut-offs for clinical relevance and

variation in answering categories in some rating scales is also suboptimal [274]. Finally, as individual items vary considerably across scales [66], it is difficult to compare the results of studies based on different scales. For future studies on individual symptoms, it is essential to increase the quality of assessment, for instance with a novel scale which assesses individual symptoms with multiple items [69]. The development of such a scale offers the opportunity to adopt a multidimensional approach in which there is attention for symptoms that have empirically or historically been highlighted but are not included in current classification systems (e.g., the frustration and embarrassment which were frequently described by patients with persistent physical symptoms [Chapter 8]) [54,236,403].

Directions for research

This thesis postulated several hypotheses to explain the relation between depressive, anxiety and somatic symptoms. More prospective studies are needed to determine whether these mechanisms indeed explain the co-occurrence. In contrast to generalizing mechanisms to all patients with depressive, anxiety as well as somatic symptoms, it should be considered that it is also possible that the mechanisms explain the co-occurrence in specific individuals and contexts. We found that patients recognized this heterogeneity as their described relations between persistent physical symptoms and emotions in consultations differed across persons, symptoms and situations (Chapter 8). That explanations can be person- and symptom-specific has also been empirically confirmed. Ecological momentary assessment studies have indicated that low mood has a stronger temporal association with fatigue than stress [439], and that this association with stress is strong in some individuals but absent in others [440]. This specificity of mechanisms stresses that it is key to identify which explanations fit which patient, for which ecological momentary assessment has significant potential [441].

A second issue that should be considered is that not isolated mechanisms, but rather the cumulative effects of their dynamic interplay may lead to the co-occurrence of depressive, anxiety and somatic symptoms. This dynamic conceptualization of medicine has an intuitive fit with clinical reality [442]. For instance, it could explain that some patients are stable for a long time but relapse very rapidly after a relatively minor event in their life [443-446]. Although this complex system approach is gaining attention in the literature, empirical support remains sparse. One promising validation method is to search for the heavy-tailed data distribution that is characteristic for a complex system [295,296,447]. This distribution is in line with that depressed patients have either low or high symptom levels [448], but has to our knowledge never been studied for anxiety and somatic symptoms. Second, according to the complex systems theory, the co-occurrence of depressive, anxiety and somatic symptoms is more likely to occur in persons with

stronger cross-connections in a network between these symptom domains than persons with weaker cross-connections [449]. Studying whether the strength of cross-connections is associated with the development of the co-occurrence of depressive, anxiety and somatic symptoms, both across persons and within persons over time, is therefore an interesting validation method [444]. The principles of the complex system approach can also be applied to patients' consultation patterns, for instance by using complexity measures (Chapter 7) [295,299]. An interesting topic is if patients with a more complex (i.e., more diverse) consultation pattern have a higher risk of sudden bursts of consultations than persons with a less complex consultation pattern.

As network analysis is a novel approach in research, many topics remain open for study. Firstly, network studies that have so far been conducted have mainly focused on symptoms and, as such, often ignored the potential effects of external factors. Recently, statistical methods have been developed to combine symptoms with external factors in one network [450]. By combining symptoms as well as external factors such as biological, psychological, social and existential factors in one multi-layered hybrid model [407,408], it is possible to identify common underlying constructs, direct symptom-symptom interactions, and shared risk factors that might play a significant role in the relation between depressive, anxiety and somatic symptoms. Authors have so far also focused on networks within persons, while interactions among people could influence this [451]. Therefore, future studies could focus on the way a network of a person is affected by a higher-order system of interacting people, ranging from the impact of a head-to-head conversation with a physician to cultural influence. Furthermore, the network approach has been introduced with symptoms and external factors with negative influence as elements of the system [55,452,453]. However, positive sensations and prognostically favorable external factors are indispensable parts of daily life and the symptom's development [454,455]. Therefore, they should be included in network models too. Besides that this would provide a richer overview of the dynamics within a person, it could also help to highlight the positive sides of elements that are typically depicted as negative in medicine. For instance, depressive symptoms have been claimed to help people solve complex problems by minimizing disruption of rumination and sustaining analysis of the problem [456].

Although statistical methods for the construction of networks can help to *explain* processes underlying symptoms, it should be considered that symptoms and their underlying mechanisms constitute a personal experience and have a meaning and a purpose to people. How factors are observed by the outside world reflects different patient realities and meanings, which are highly relevant in clinical care [408,457]. To gain more insight into this *understanding* of symptoms and their underlying mechanisms, it is important to combine a quantitative focus with qualitative methods, for example by

analyzing patient's narratives [458,459]. This becomes apparent from the way patients described persistent physical symptoms and emotions in consultations (Chapter 8). Although these types of symptoms are seen as distinct categories in the medical realm, some patients completely integrated the two in their narratives. It should therefore be kept in mind that the way a typical network model is set up (i.e., with individual symptoms) may not compel with the view of each patient. In order to align with the patient in ecological momentary assessment, it would be best to discuss such assumptions beforehand and adjust the questionnaire to the patient's point of view.

Although clinical guidelines typically recommend the use of symptom management strategies, antidepressants or cognitive behavioral therapy for patients with depressive, anxiety and somatic symptoms [289,460,461], little is known about which of the options has the highest efficacy for particular patients. While we have considered the symptom-specific effects of antidepressants and psychotherapy in persons with a primary depressive disorder, future research could focus on: a) the effects of other interventions, on b) a broader spectrum of symptoms, in c) patients with co-occurring depressive, anxiety and somatic symptoms. One interesting comparison would be the relative efficacy of varying types of antidepressants. Although it is common knowledge that TCAs are more effective for pain symptoms but have more anticholinergic side effects than SSRIs [462,463], less is known about their relative effects on other specific depressive, anxiety and somatic symptoms. Studies focusing on the effects of such drug classes on more types of symptoms could help to increase insight into which interventions may be most effective for which patients with co-occurring depressive, anxiety and somatic symptoms.

A future perspective

In the historical perspective, it became apparent that numerous conceptualizations of the relation between depressive, anxiety and somatic symptoms have dominated the medical realm throughout history [1]. In recent decades, the biopsychosocial model has attempted to supersede the reductionist biomedical model, but has not fully succeeded [5]. Many authors have called for a multidimensional, multifactorial and dynamic conceptualization of medicine [8,55,446,464,465]. The complex systems approach in the network perspective may be this conceptualization. It abandons categorical classifications, allows for the consideration of factors from many different levels (e.g., biological, psychological, social, existential levels) and provides a rationale for the non-linear development of pathology [15]. Furthermore, in this discussion we explained that the approach might help to enhance patient-centered communication and personalization of treatment. As such, it may be the key to increase knowledge about the co-occurrence between depressive, anxiety and somatic symptoms, both regarding its epidemiological

and clinical aspects. The promise of the approach is reflected in the booming literature on its conceptualizations and potential applications [94]. More of such work is needed in order to investigate the basic assumptions and statistical underpinnings of the approach. Currently, however, the most important challenge lies in the translation of the conceptual model to everyday clinical practice for physicians.

A final note

We end this thesis by taking a step back. The way we view depressive, anxiety and somatic symptoms is not static. Theories changed throughout history: somatic theories originated in physically-oriented Antiques medicine, machine-like theories were created in the Industrial Age, and brain disease theories thrived together with brain investigations [1]. In this context, the complex system theory fits well with the 21st century's focus on complex systems among people via social media, economies via import and export and countries via flight paths. Similarly, where previous labels suggested a biomedical underlying mechanism ("hysteria" was derived from the Greek word for uterus), labels from the current imaging era tend to emphasize what is or is not observed ("medically unexplained symptoms" or, more recently, "persistent physical symptoms") [1]. That approaches in medicine are subject to changes teaches us that our conceptualization resembles a well substantiated mind map more than the reality. This map is an indispensable basis to get a grip on reality and to shape health care. However, we should not lean too heavily on it. Instead of imposing our medical conceptualizations and labels on patients, we should listen to their ideas and engage in a dialogue to formulate explanations together. This interplay between the patient and the physician designs the most fruitful body-mind maps.