Chapter 7

General Discussion

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Preface

This thesis focused on tackling the heterogeneity of major depressive disorder (MDD). MDD patients differ strongly from each other in terms of their etiology, course of illness and symptom presentations, which hinders research and optimal treatment prescription. Suggested clinical subtypes of MDD thus far have not solved this issue. Alternative data-driven approaches have been applied to identify MDD subtypes based on similar patterns in symptom data, but conclusive results have not yet been obtained. These issues may be due to the fact that data-driven approaches applied so far have not incorporated all major sources of depression heterogeneity (persons, symptoms and time-points) in one model. Therefore, to enhance our understanding of MDD, this dissertation was aimed to study the heterogeneity of depression at all three levels simultaneously: identifying more homogeneous entities of MDD at each level.

In this chapter, I will discuss the presented findings and will try to put them into perspective by evaluating the findings’ clinical and methodological implications. First, the main findings will be summarized (section 1) and further discussed in terms of clinical implications (section 2) and methodological implications (section 3). Subsequently, the strengths and limitations of the thesis will be discussed (section 4). The dissertation is closed by a discussion of future research (section 5) and concluding remarks (section 6).

Summary of the main findings

MDD symptoms can be decomposed into two homogeneous constructs (the ‘mood-cognition’ and ‘somatic’ domains), each of which is associated with specific patterns of prognostic factors, course-trajectories and long-term outcomes.

The first study aimed to identify data-driven MDD course-groups to establish more specific prognostic and etiological models of MDD by addressing symptom heterogeneity (Chapter 2). To this end, a parallel processes latent class growth analysis (PP-LCGA) was applied, which resulted in the identification of groups of patients that either persisted on ‘mood-cognition’ (MC) or ‘somatic’ (SOM) symptoms. These subgroups showed distinctive associations with prognostic factors and long-term outcomes, indicating that symptom-specific course prototypes could be used in the prediction of specific patterns of depressive symptom persistence in clinical settings. This study accounted for heterogeneity across patients while addressing symptom- and time-level heterogeneity and the results indicated that such an approach could lead us to more specific prognosis and etiology. However, the PP-LCGA approach does have some disadvantages,
the most notable being that it is based on discrete subgrouping with latent classes and does not allow for heterogeneity within identified subgroups. This means that patients with persisting MC or persisting SOM are assumed to be homogeneous within each cluster. This might be too strong an assumption, as it basically implies that all person-level heterogeneity can be explained by a very limited number of classes. More importantly, this approach does not align well with the many real-life observations that psychopathology is not a discrete, but a continuous phenomenon [1, 2]. This motivated further investigations and evaluations of 3MPCA as an alternative, dimensional approach to incorporate all sources of heterogeneity (person, symptom and time) and their interactions into a single model.

**By simultaneously decomposing depression heterogeneity at the person-, symptom- and time-level, distinguishable components were found on each level as well as interesting interactions between the different levels’ components.**

In Chapter 3, the three major sources of MDD heterogeneity were analyzed simultaneously and included in a model by means of Three-mode Principal Component Analysis (3MPCA). The results showed that symptoms (measured with the BDI) could be decomposed into two symptom-level components (‘cognitive’ and ‘somatic-affective’). In addition, the nine consecutive time-points were decomposed into two time-level components (‘improving’ and ‘persisting’). Persons could be decomposed into three person-level components, each characterized by different symptom-by-time interaction patterns (‘severe non-persisting depression’, ‘somatic depression’ and ‘cognitive depression’). Interestingly, the identified three person-level components were associated differently with a range of external variables (i.e. that were not included in model building). ‘Severe non-persisting depression’ was correlated positively with baseline psychopathology (r=0.60) and negatively with quality of life (r=-0.50), ‘somatic depression’ was correlated negatively with physical functioning (r=-0.45), and ‘cognitive depression’ was correlated positively with neuroticism (r=0.38) and negatively with self-esteem (r=-0.45). These results served as a proof of principle for the utility of the technique to investigate the underlying structure of complex psychopathology data and suggested that 3MPCA could help future development of better empirical depression subtypes.

**The long-term prognostic value of 3MPCA components was higher than those of traditional latent variable models and prognostic factors.**

In Chapter 4, the added prognostic value of the 3MPCA components (identified in Chapter 3) for long-term depression outcomes was investigated by evaluating their predictions of 3- and 11-year follow-up scores on the BDI in the same dataset.
To gain insight into the added value of 3MPCA-based components over and above more traditional predictors and data-driven models, the predictive value of 3MPCA was compared with that of traditional latent variable models (e.g. Principal Component Analysis [PCA], Latent Class Analysis [LCA], and Growth Mixture Model [GMM] and prognostic factors such as baseline MDD severity and personality). The results showed that the 3MPCA components predicted 41% and 36% of BDI-score variance at 3 and 11-year follow-up, respectively, whereas previously used latent class models or predictors explained 4 to 32% and 3 to 24% of BDI variance at 3- and 11-year follow-up, respectively. These findings implied that accounting for the three sources of heterogeneity in a longitudinal study improves the longer-term predictions of depression severity, underlining the potential of this approach for developing better prognostic models. Still, the study included a relatively small MDD outpatient sample (N=200) that was also used to evaluate the estimation and usefulness of 3MPCA in the first place. In addition, no associations between the 3MPCA components and treatment were found. Therefore, the clinical use of 3MPCA was further investigated in a larger sample to see if 3MPCA can be used to explain heterogeneity in treatment response.

3MPCA offers an insightful longitudinal description of the most important sources of variation in antidepressant treatment response, providing interesting leads for clinical research into empirically-based antidepressant prescription. Antidepressants are commonly used treatment for MDD patients, but only part of the patients react favorably to the treatment. Identifying which patients may benefit from antidepressant treatment has been shown to be difficult. In Chapter 5, it was hypothesized that this may partly be due to the fact that the inter-individual differences in course trajectories on different symptomatology have not been properly modeled and considered in previous studies. Therefore, 3MPCA was used to capture and investigate dynamic variations of antidepressant treatment response in the study described in Chapter 5. The results showed that the symptoms could again be decomposed into two symptom-mode (‘cognitive’ and ‘somatic’), time-points could be decomposed into two time-mode components (‘first measurements’, ‘last measurements’) and that persons could be decomposed into three person-mode components, each characterized by different symptom-by-time interactions and correlations with external measures (‘negative/suicidal thoughts’, ‘physical dysfunction’ and ‘general improvement’). Interestingly, the ‘Negative/suicidal thoughts’ and ‘Physical dysfunction’ person-component scores were negatively associated with remission and ‘Physical dysfunction’ person-component scores were further correlated with side-effects (r=0.34-0.37) and long-term severity, whereas ‘General improvement’ scores were positively associated with remission. As such, 3MPCA showed how patients
differ in their response to treatment and offered an insightful longitudinal description of the different ways in which patients respond to antidepressants. This is important, as more knowledge about how different types of patients show different response patterns could foster new clinical research into empirically-based antidepressant prescription. Notwithstanding the usefulness and importance of incorporating three sources of heterogeneity in one model to account for depression heterogeneity with respect to long-term outcome and treatment response, the findings in Chapters 2 to 5 did not address two major issues. First, depression and anxiety are highly comorbid and symptoms of the disorder groups show much overlap. Because depressive and anxiety symptoms co-occur so often in patients, in order to further validate the added value of the 3MPCA approach to decompose heterogeneity among patients, data on both depressive and anxiety symptoms needed to be analyzed. Second, the analyses so far did not include any biological variables (i.e. biomedical measurements, biomarkers) due to the used study designs. Since 2010, the US National Institute of Mental Health developed a research framework, Research Domain Criteria (RDoC), which aims to understand mental disorders by validating findings from biological perspective. Given this research agenda, the extent to which 3MPCA-derived components are associated with biological factors was further evaluated.

**Depression and anxiety heterogeneity could be explained by three symptom-mode components (‘anxious-arousal’, ‘anhedonia’ and ‘mood-cognition’), two time-mode components (‘improving’ and ‘persisting’) and four person-mode components (‘anhedonic’, ‘somatic’, ‘cognitive’ and ‘recovery’). No substantial correlations were found between the person-mode components and a range of biomarkers.**

In Chapter 6, 3MPCA was applied to longitudinal measurements on a range of depressive and anxiety symptoms. The results showed that the large symptom-pool could be decomposed into three symptom-mode components (‘anxious-arousal’, ‘anhedonia’, ‘mood-cognition’) and that the time points could be decomposed into two time-mode components (‘improving’, ‘persisting’). In addition, persons were decomposed into four person-mode components (‘anhedonic’, ‘somatic’, ‘cognitive’ and ‘recovery’) that each showed different patterns of symptom-domain scores over time and external correlations. The ‘anhedonic’ person component had persisting ‘anhedonia’ symptom and low extraversion (r=−0.42), the ‘somatic’ person component had persisting ‘anxious-arousal’ symptom and increased insomnia (r=0.35), the ‘cognitive’ person component had persisting ‘mood-cognition’ symptom and high neuroticism (r=0.70), and the ‘recovery’ person component showed quick recovery of all symptom domains. Although blood and saliva markers were significantly
associated with the resulting person-mode components, only small (≤0.19) correlations were found.

**Main Findings in perspective**

The aim of this dissertation was to study the heterogeneity of depression and to enhance our understanding of MDD. In this section, I will combine the main findings and further discuss their clinical and methodological implications.

*Depressive symptoms may be better understood as a compound of different symptom domains, including a ‘Cognitive’ and ‘Somatic’ symptom-domain.*

In line with previous studies [3-7], the presented studies repeatedly found ‘cognitive’ and ‘somatic’ symptom domains, despite of the differences in study designs and analyses (Chapters 2-6). Previous studies using Factor Analysis (FA) or Principal Component Analysis (PCA) on DSM criterion symptoms of MDD have found varying results with regard to the number of symptom sub-domains, ranging from 2 to 7 factors [8]. However, many cross-sectional factor-analytical studies that covered more than just the nine DSM criterion symptoms (i.e. depression questionnaires) showed a distinction between ‘cognitive’ and ‘somatic’ symptom domains, similar to those found in Chapter 3 [3, 9, 10]. The fact that a similar structure was also observed within the 3MPCA model framework suggests that the ‘cognitive’ and ‘somatic’ symptom-component structure is important and stable not only for cross-sectional, but also for longitudinal depression data. When the study population was extended from those with MDD to those with a 1-month diagnosis of depression and/or anxiety, ‘anxious-arousal’, ‘anhedonia’ and ‘mood-cognition’ symptom components were identified (Chapter 6), which are seemingly different from ‘cognitive’ and ‘somatic’ symptom domains. However, this may due to the fact that the symptoms measured in Chapter 6 contained a broader and extensive range of anxiety-related somatic arousal symptoms, such as ‘face flushed’ or ‘feeling hot’ and a range of items specifically measuring lack of positive affect. As a result, a broader range of symptom-mode components was found.

Besides their distinctive phenotypes within the structure of depressive symptoms, previous studies have shown the two symptom domains (‘cognitive’ and ‘somatic’) to be differentially associated with a range of clinically important factors. The ‘cognitive’ symptom domain has been shown to be associated with increased neuroticism, decreased extraversion and increased psychiatric comorbidity [11], whereas the ‘somatic’ symptom domain has been shown to be associated with somatic risk factors [12] and somatic disease [13]. Similar
patterns of associations were also found in Chapter 6, where the ‘cognitive’ person-mode component was characterized by persistent ‘mood-cognition’ symptom scores and associated with higher neuroticism, decreased extraversion and increased rates of diagnoses of depression and anxiety disorders, while the ‘somatic’ person-mode component was characterized by high persistent ‘anxious-arousal’ symptom scores and associated with somatic disease (mainly metabolic symptoms). Interestingly, in Chapter 4, ‘cognitive’ symptom scores were predicted with higher accuracy than ‘somatic’ symptom domain scores at 3 and 11 years follow-up, indicating that ‘cognitive’ symptom scores are comparatively stable. This could reflect the strong link between these symptoms and the personality trait neuroticism, which is known to be relatively stable within persons [14].

Taken together, these findings indicate that, within the construct of depression, ‘cognitive’ and ‘somatic’ symptom domains represent entities with different underlying mechanisms and clinical characteristics. The fact that the depression construct was found to be a compound of ‘cognitive’ and ‘somatic’ symptoms raises a question with regard to the current depression measurement system where depressive symptoms are assumed to equally contribute to a unidimensional depression severity construct and are simply summed up to a single severity score [15].

The importance of incorporating three sources of heterogeneity (person, symptom and time) in one model was underlined by the finding that the resulting models show meaningful associations with long-term outcome, antidepressant-treatment response and co-occurrence of depression and/or anxiety disorders.

Some first indication of the added value of incorporating three sources of heterogeneity in a single dimensional model was given in Chapter 2, where components were shown to have different patterns of correlation with different external variables. Importantly, Chapter 3 showed that the components had the highest predictive value for long-term depression outcomes, when compared to traditionally-used prognostic factors and data-driven models (PCA, LCGA, LCA). Moreover, the usefulness of incorporating three sources of heterogeneity in one model was further confirmed with respect to predicting treatment responses (Chapter 4). These findings illustrate that integrating the three sources of depression heterogeneity in one model yields a comprehensive set of scores that can capture various clinical characteristics. This fits in with previous findings showing distinct symptom domains (‘cognitive’ and ‘somatic’) [16-18] and their dynamics [19-21] to be differentially associated with long-term depression prognoses.
Revised symptom measurements contain more information that can be used to differentiate between patients and hold more predictive value for long-term depression outcomes than single symptom measurements.

Several of the chapters showed that incorporating variations over time on a range of symptom-measurements provided a very effective way to differentiate between patients with different phenotypes and, more importantly, different outcomes. This was reflected in the large explained variances found in the ‘follow-up’ time-mode component in the core arrays, indicating that the temporal aspect captures an important part of depression heterogeneity. In addition, as stated above, the 3MPCA models, which incorporate the temporal aspect of depression, were shown to be superior predictors of long-term outcome of depression, compared to cross-sectional predictors. This is in line with previous studies [22, 23] where follow-up measurements were shown to have higher long-term predictive value, compared to baseline measurements. Although much attention has been paid to the associations between baseline severity and prognosis of depression [24-27], the presented results indicate that investigation of repeated depression symptom assessments over time could lead not only to a better understanding of depression heterogeneity, but eventually also to better outcome predictions. This aligns with previous research that has investigated the use of multiple repeated diary assessments to predict treatment response and outcomes (e.g. [28]). The presented results are based on repeated assessments on a larger time-scale, but also point towards the importance of incorporating repeated measures in diagnostic assessment procedures.

A dimensional approach, as applied by 3MPCA, allows for a better and more precise description of variations in psychopathology.

The current categorical DSM diagnostic system assumes ‘a point of rarity’ between psychiatrically ill and healthy individuals [29]. As discussed in Chapter 1, this artificial distinction has brought marked advantages to the field of psychiatry, but also a range of serious disadvantages, which have hampered research into the underlying mechanisms of mental health [30-32]. For this reason, an alternative dimensional view of psychopathology has been suggested [29]. Thus far, the majority of dimensional research has been focused on identifying multi-dimensional symptom structures on a phenomenological level [33-36]. However, studies have also shown that using a dimensional approach is more optimal in etiological [12, 37] and clinical [18, 37] research, compared to the categorical view (e.g. DSM-categories). There are two major advantages to a dimensional approach. First, a dimensional approach allows us to investigate more complex and subtle underlying processes since symptom severity is used as
a continuous, quantitative variable, whereas a categorical or dichotomous approach only allows for simple group-comparisons. Second, a dimensional approach enables us to include the whole population in psychopathology research since all individuals are positioned somewhere along the underlying severity dimension. Therefore, unlike the current categorical diagnostic system, which labels ‘sub-threshold’ individuals as mentally healthy, a dimensional approach allows for investigation and inclusion of psychopathology severity at all levels, ranging from low, through sub-clinical to clinical. This is advantageous since persons that do have symptoms but do not meet full DSM criteria for a diagnosis (i.e. ‘sub-threshold’ individuals) are known to be at increased risk of later development of psychiatric disorders and increased healthcare use [38, 39].

By using the 3MPCA approach, the current thesis adheres to a dimensional view on psychopathology, i.e. each of the person-, symptom- and time-level component structures are assumed to be continuous and (multi)dimensional. Indeed, Chapter 2 showed that symptoms were decomposed into two dimensional domains and this was further extended to the person-, symptom- and time-level in Chapter 3 through Chapter 6. The resulting components in Chapter 3 through Chapter 6 provided more detailed insights into the many variations that are possible within the depression construct. Importantly, in 3MPCA, persons were not split up into discrete groups of persons (as in LCA), but each got a score on each of the person-mode components. The pattern of these scores provides a dimensional description of a persons’ specific phenotype: i.e. how his/her different symptom-domains develop over time. Although this means that persons cannot be put into subgroups with neat boundaries, the person-mode component scores do provide for a description of inter-personal differences that better aligns with the continuous nature of psychopathology than the use of a limited set of subgroups.

Implications for the Research Domain Criteria (RDoC): Phenomenological depression and biomarkers may be two distinct worlds that are only weakly associated.

In 2010, the National Institute of Mental Health introduced ‘Research Domain Criteria (RDoC)’, a project to develop ‘new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures’ [40]. Despite the enormous efforts that have been made so far, such a diagnostic system for psychiatric disorders is still to be found. In Chapter 6, we examined the possibility to link biological variables to person-mode components. The results indicated possible associations of the ‘anhedonic’ and ‘somatic’ person components with biological variables, including metabolic markers, such as high blood pressure and BMI. However, the person-mode component indicating severe
and persisting ‘cognitive’ depression and anxiety symptoms, i.e. the ‘cognitive’ person-mode component, was not strongly associated with any of the tested biological variables. These different patterns of association could point towards a specific role of metabolic disturbances in those patients with persistently high ‘anhedonia’ and ‘somatic’ symptoms. This aligns with previous research that has shown metabolic disturbances to be involved in depression in particular subgroups of patients [41]. However, given the large amount of symptomatic variance captured by the 3MPCA components and the observation that the tested biomarkers in Chapter 6 showed no or weak associations with the person-mode components, it seems that the majority of variance in depression symptomatology is not explained by variations in biomarker. Based on this, one could state that the phenomenology of depression and biomarkers represent two distinct worlds that can hardly be linked to each other. This is likely to be due to the fact that there is no absolute measure to determine the presence of a depressive symptom. Typically, depression symptoms are measured by self-report, using a discretized Likert response scale. In such an approach, it is unavoidable that measurements contain a large measurement error, and thus, only partly reflect the presence of symptoms. In addition, currently available biomarker measurements are also rough estimates of true levels due to limitations of the used technologies, and the measures are affected to some degree by human errors. Thus, both for symptoms and biomarkers, measurements can only be seen as distal representations of the true levels. Moreover, it is highly likely that many layers of pathophysiological and psychological processes lie between the actual biomarkers, the experience of symptoms, and the subsequent reporting of symptoms. All of this makes it less likely that strong associations will be found between measures of biomarkers and symptoms.

The three-way interactions between person, symptoms and time-components seem to explain a sizable part of the total variance, but a greater part is explained by the general downward trend over time in severity in the used patient datasets.

Across the different study samples, the 3MPCA model explained 26-29% of the total variance in symptom scores over time (Chapter 3, 5 and 6). This indicates that the model explains a considerable part of the variance with the decomposition of the person-, symptom- and time-mode. However, the total explained variances increased remarkably in all studies (65%, 81% and 91% for Chapter 3, 5 and 6, respectively) once the ‘general trend’ was incorporated into the model (where the 3MPCA model reflects the variations up-and-above this trend). The reason for this finding could be that all investigated samples were patient-samples, which are bound to show a strong improvement over time by default. As a result, an
important part of the variation in the longitudinal follow-up measurements can be explained by a downward trend that is common to roughly all patients, leaving additional variations around this trend to be explained. The 3MPCA results showed that this additional variation among patients often manifested itself in the relative persistence of one particular kind of symptoms. This is interesting, as it provides insight into the different kinds of symptom persistence that can occur in patients, even when they all seemingly show improvement in their overall severity levels.

**Clinical implications**

*Clinical use of a dimensional approach: use of the person-mode component scores.*

Although the benefits of using dimensional approaches in psychopathology research have often been addressed [42], incorporation of a dimensional approach in clinical practice has not yet been fully attained. This is because the evidence for the validity and clinical usefulness of dimensional models is presently too limited [43] to merit a paradigm-shift in psychiatric diagnostics [44]. This thesis contributes to the ongoing research on the validity and usefulness of dimensional models and the results did indicate the clear added value of a dimensional approach for describing interpersonal variations in clinical features among patients (Chapter 2 through Chapter 6). However, 3MPCA results are rather abstract and counter-intuitive to some, making translation to possible clinical implementations quite hard. Still, there is a lot to be learned from the results. Therefore, the possibilities to use results from 3MPCA modeling to potentially improve clinical practice will be discussed next.

The person-mode component scores for a particular patient can be seen as a profile that specifically reflects a person’s characteristics, analogue to how a pattern of personality trait scores reflects a person’s personality structure. Therefore, the person-mode component scores could be used as a diagnostic description of a patient, which could be used as a tool to formulate a prognosis and a treatment plan. For example, in Chapter 6, there were four person-mode components (‘anhedonic’, ‘somatic’, ‘cognitive’ and ‘recovery’) and three symptom-mode components (‘anxious-arousal’, ‘anhedonia’ and ‘mood-cognition’). To exemplify a possible clinical use of the derived component scores, five subjects analyzed in Chapter 6 were selected for further inspection. The patients’ baseline characteristics are summarized in Table 1, while their person-mode component scores and symptom-domain scores are plotted in Figure 1 and Figure 2, respectively.
Table 1. Baseline characteristics of the selected five patients

<table>
<thead>
<tr>
<th>ID</th>
<th>Gender</th>
<th>Type of care</th>
<th>Age</th>
<th>Lifetime diagnosis of MDD</th>
<th>Lifetime diagnosis of GAD</th>
<th>Number of MDD episodes</th>
<th>Anxiety diagnosis at baseline</th>
<th>Depression diagnosis (6M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>Primary</td>
<td>51</td>
<td>Yes</td>
<td>No</td>
<td>20</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>Specialized*</td>
<td>51</td>
<td>No diagnosis</td>
<td>No diagnosis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>Primary</td>
<td>38</td>
<td>No diagnosis</td>
<td>No diagnosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>Primary</td>
<td>59</td>
<td>Yes</td>
<td>No diagnosis</td>
<td>1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>Primary</td>
<td>59</td>
<td>Yes</td>
<td>No diagnosis</td>
<td>20</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note that the average line indicates the 'general trend', i.e. a patient who scored exactly average on each item on all time points.

Looking at Table 1, Figure 1, and Figure 2, it is possible to discern patients with clearly different clinical characteristics. For example, Person 1 had her highest score on the 'anhedonic' person component, indicating comparatively high persistence of anhedonia (Figure 1), as reflected in persistently high 'anhedonia' and lower scores on 'anxious arousal' and 'mood-cognition' symptom domains.

Given that this person component was found to be associated with chronicity and with high neuroticism and low extraversion, patients with a high score on this particular component could require special attention to their cognitive/anhedonic symptomatology and vulnerable personality structure during (psycho-social) treatment.

Person 4 had his highest score on the 'anhedonic' component followed by the 'somatic' person-mode component. Indeed, Figure 2 showed this patient to have increasing 'anhedonia' symptom scores over time, and to a lesser extent, increasing 'anxious-arousal' scores over time. Given that these person-mode components were associated with increased insomnia and high BMI, a clinician could pay extra attention to the possible presence and adverse effects of metabolic dysregulation and the need to manage and/or treat insomnia.

Person 5 showed a clearly different clinical characteristic. For example, Person 5 had the highest score on the 'cognitive' person-mode component and Figure 2 showed indeed showed this person to have comparatively high persisting 'anhedonia' and 'mood-cognition' symptoms.

Given that this person component was found to be associated with chronicity and with high neuroticism and low extraversion, patients with a high score on this particular component could require special attention to their cognitive/anhedonic symptomatology and vulnerable personality structure during (psycho-social) treatment.
Looking at Table 1, Figure 1 and Figure 2, it is possible to discern patients with clearly different clinical characteristics. For example, Person 1 had her highest score on the ‘anhedonic’ person component, indicating comparatively high persistence of anhedonia (Figure 1), as reflected in persistently high ‘anhedonia’ and lower scores on ‘anxious arousal’ and ‘mood-cognition’ symptoms over time (Figure 2). Person 2 had her highest score on the ‘somatic’ person component, which is further illustrated in Figure 2 where Person 2 showed a persistently high score on the ‘anxious-arousal’ and lower scores on the ‘anhedonia’ and ‘mood-cognition’ symptom domains. Each of these patterns could be associated with different prognoses and treatment needs. For instance, in Chapter 6, the ‘somatic’ person-mode component was found to be associated with increased insomnia. Therefore, the clinician could take into account the possibility of having to treat insomnia. Person 3 showed her highest score on the ‘cognitive’ person-mode component and Figure 2 showed indeed showed this person to have comparatively high persisting ‘anhedonia’ and ‘mood-cognition’ symptoms. Given that this person component was found to be associated with chronicity and with high neuroticism and low extraversion, patients with a high score on this particular component could require special attention to their cognitive/anhedonic symptoms and vulnerable personality structure during (psychosocial) treatment. Person 4 had his highest score on the ‘anhedonic’ component followed by the ‘somatic’ person-mode component. Indeed, Figure 2 showed this patient to have increasing ‘anhedonia’ symptom scores over time and, to a lesser extent, increasing ‘anxious-arousal’ scores over time. Given that these person-mode components were associated with increased in insomnia and high BMI, a clinician could pay extra attention to the possible presence and adverse effects of metabolic dysregulations and the need to manage and/or treat insomnia. Person 5 showed a
high score on the ‘recovery’ person-mode component with a considerable level of ‘cognitive’ person-mode scores, which is reflected in Figure 2, where decreases are seen on all symptom domains, indicating quicker recovery than the ‘general trend’. This could be associated with an increased number of MDD episodes (Table 1) compared to other patients, i.e., this patient may show quick recovery, but due to the high level of ‘cognitive’ person score, this patient may suffer from relapse. Although these plots are based on a very long follow-up period and measurements at yearly intervals, they do show how dimensional scores derived from 3MPCA could be used in devising diagnostic tools. In practice, the follow-up time should be shorter (e.g. 4-8 weeks) and measurements closer together (e.g. weekly; twice per week), but the implementation could be very similar to the method described above.

Methodological implications

In this thesis, 3MPCA was extensively applied (Chapter 3, 5 and 6) in search of the underlying component structure of complex multifactorial depression data. In this section, the use and usefulness of 3MPCA in such data will be discussed in more detail.

The application of 3MPCA (also known as Tucker 3, Three-mode factor analysis, Three-way component analysis) has been rather common in environmental research [45], image processing [46], chemistry [47, 48], medical data [49] and psychology [50-52], but has not been used extensively in psychiatric data. This thesis provides a proof-of-principle for the usefulness of 3MPCA in this setting: the resulting components were shown to provide insightful descriptions of depression heterogeneity (Chapter 3), to predict long-term depression outcomes (Chapter 4), and to explain heterogeneity in depressive course during treatment (Chapter 5). Given that the 3MPCA model assumes a multicomponent structure within each mode of the data, it is not surprising that 3MPCA models fit well to psychiatric data, as the assumption of multidimensionality fits well to the nature of psychopathology.

Although advantages of the use of 3MPCA in psychiatric data have been emphasized in this thesis, it should be noted that not all psychiatric data will be suitable for 3MPCA modeling. As discussed above, 3MPCA captures variations around the ‘general trend’ in the data (i.e. a three-way interaction). Therefore, when longitudinal data is relatively stable over time and no interaction occurs between persons, symptoms and time, other techniques (such as applying PCA to data collected at one measurement time point) would be more suitable than 3MPCA. For this reason, it is best to evaluate if and to what extent a three-way
interaction underlies the variance in the data, by performing a three-way Analysis of Variance (three-way ANOVA) before using 3MPCA.

As shown in the previous section, 3MPCA models could provide clinically relevant information by means of their person-mode component scores. However, 3MPCA is a technique to summarize a given longitudinal dataset. If symptom scores of a new patient are available, a clinician might be interested in using these scores to make a prediction about his/her symptom course trajectories. In order to translate the current findings to such a setting, a technique to estimate his/her person-mode component scores would be required. In theory, this could be done by fixing the symptom- and time-mode components and the core array, and applying an Ordinary Least Squares regression. However, this is a topic in need of further research.

**Strengths and limitations**

**Limitations**

**Data limitations**

Our findings are limited by the nature of the used datasets, which varied with regard to the included symptoms, the number and spacing of the measurement time points, and the type of outcomes and biological variables. The datasets analyzed in Chapter 2 and Chapter 3 were relatively small (N<300), which might have limited the accuracy of the predictions (Chapter 4). The STAR*D sample was relatively large (N=1,656), but included only patients treated with escitalopram, which limits the generalizability of the findings to other patient samples (Chapter 5). The generalizability of the findings in Chapter 6 are limited to patients with a one-month diagnosis of depression and/or anxiety disorders. None of the used samples included very severe patients or inpatients.

Another limitation could lie in the symptom measures used in this thesis. Typically, symptom severity was measured with Likert scales, with a limited range of scoring options. Therefore, the findings may be influenced by the discrete nature of the data and by possible floor or ceiling effect. More detailed severity scores (e.g. from 0 to 100) could enable more precise estimations.

Finally, the studies in this dissertation did not find any clear and strong associations between the person-mode component scores and important subject groupings (e.g. gender or type of care). A reason may be that the studies lacked power (i.e. small sample size) or the data had large measurement errors, which is customary with self-reported psychological data. However, it is also possible that the lack of concordance between bottom-up data-driven person-components and
top-down imposed groupings reflects the fact that psychopathology variations are better captured by dimensions rather than discrete categories.

**Methodological limitations**

Although the use and usefulness of the results of 3MPCA were underlined in this thesis, the component structures should be interpreted carefully. In this thesis, orthogonal rotation (Orthomax rotation [53]) was applied to obtain simple structure in 3MPCA, whereas the assumption of uncorrelated components for each mode may be too strict to do justice to the actual nature of psychopathology. This approach was used because there is no available oblique rotation technique, which allows for obtaining simple structure in the core array as well as in all three modes.

**Strengths**

The work presented in this thesis also has several strengths. First, the presented studies were the first to simultaneously decompose depression heterogeneity by incorporating all available data and considering all three sources of heterogeneity in one model, without imposing top-down, a priori constraints on the component structure. The inclusion of many data points and the lack of a priori assumptions ensured that all relevant variance in the collected data could be captured and investigated. Second, the resulting components were associated with clinically relevant outcomes, such as treatment response, long-term prediction and biological variables, making it possible to evaluate the actual ability of the 3MPCA model to differentiate between different clinical pictures. Third, the internal validity of the components was tested by a split-half procedure in Chapter 3 through Chapter 6. Moreover, missing values, which are almost inevitable with longitudinal data, were imputed by multiple imputation. Apart from the advantage of not having to exclude cases form the analyses, the use of multiple imputed datasets had the additional advantage that it enabled investigation of the stability of model solutions.

**Future research directions**

The presented results offer several leads for further research. First, 3MPCA was used in an exploratory way and the generalizability and validity of the presented findings need to be replicated in independent samples. One way to do this could be by fitting the models to new datasets and fixing the symptom- and time-mode component scores or the core array to be exactly the same as in the previous results. However, this requires that the design, number of time-points and the instruments
are exactly the same as those used in the original study. Another way to evaluate the fit of a previously estimated 3MPCA model in a new dataset would be by putting constraints on the core array of the fitted 3MPCA model by setting zeros at fixed positions [54, 55].

Second, given the large number of depression severity measures, which consist of different symptoms (eg. BDI, IDS [56]), and given that comorbidity of depression and anxiety is the rule rather than the exception, future research could focus on a broader set of symptom assessments administered in broad groups of patients, as was done in Chapter 6. Such a cross-diagnostic approach may provide many interesting new insights that could help improve our understanding of nosology in psychiatry and to develop more personalized treatment.

**Concluding remarks**

To the best of my knowledge, this dissertation is one of the first works to address MDD heterogeneity by postulating three sources of heterogeneity and their interactions in one model and taking a completely dimensional approach to psychopathology. The results indicate that this approach allows us to gain a more integrated view of depression as a complex and dynamical construct and into the many possible patterns and trajectories of depressive symptomatology. Such insights are essential to gain a better understanding of the various sources of phenotypical variation among patients, and eventually, of how these relate to etiological mechanisms and clinical outcomes.
Chapter 7 | General Discussion

Reference

Juliet (Painted by Miho Hashimoto)