Chapter 1

Introduction
Chapter 1 | Introduction

Preface

Major Depressive Disorder (MDD) is one of the largest contributors to the global burden of disease and expected to remain so in the future due to scientific stagnation: the effects of the available treatments are unsatisfactory and identifying the cause of MDD has proven to be difficult. One important reason for this is the fact that the current definition of MDD is highly heterogeneous. Patients with MDD are diverse in terms of their clinical presentation, severity, etiology and course. Therefore, scientific endeavors have been made to work towards more homogeneous MDD subtypes, hoping that such subtypes would enable more specific linkage of clinical presentations to course predictions and underlying etiological mechanisms. However, these goals have not been attained yet. Therefore, research is needed that provides deeper insight into the heterogeneity of MDD.

Research so far suggests that heterogeneity of MDD is complex and exists at different levels of the phenotype: (1) patients, (2) symptoms and (3) course over time. Although previous studies have described heterogeneity at each of these levels separately, the three major sources of heterogeneity and their interactions have never been incorporated in a single model. As a result, the current knowledge about MDD heterogeneity has a piecemeal nature and does not easily integrate into a coherent model that captures all relevant interpersonal variations within the MDD phenotype.

The aim of this thesis is to address this issue by decomposing MDD heterogeneity by postulating three sources of heterogeneity (patients, symptoms and time) and their interactions in a single, empirically-based model. To this end, Three-Mode Principal Component Analysis (3MPCA) is applied to various longitudinal depression datasets. In this manner, the heterogeneity of depression regarding the three different sources is studied in an overarching way.

Background

Major Depressive Disorder

MDD is a mental disorder with a high global prevalence rate [1-3]. Currently, MDD is estimated to affect 350 million people in the world [4], with average lifetime prevalence rates of 14.6% in high-income countries and 11.1% in low- to middle-income countries [5]. The World Health Organization (WHO) World Mental Health surveys revealed that when averaged across all countries, 1 out of 20 people reported having had an episode of depression in the previous year [6].
The age of onset of MDD is typically in the beginning of adulthood, often followed by multiple recurrent episodes or even a chronic course during a patient’s life time [7]. Among MDD patients, recurrence and relapse-rates are high [8-10], with about 50% to 75% of patients experiencing more than one clinically significant episode in their lifetime [11] and the probability of relapse becoming higher as more depressive episodes have been experienced by a patient [12, 13].

MDD is associated with a range of negative outcomes. MDD severely reduces patients’ functioning levels in the work, school and family domains [14, 15] leading to marked levels of disability that also affect families, peers and employers. In addition, MDD is associated with higher risk of other, comorbid mental disorders (e.g., anxiety disorders [16]) and comorbidity with life-threatening somatic physical conditions (i.e., type 2 diabetes [17] and heart disease [18]). The latter is one of the reasons for increased mortality among MDD patients, but another reason is the association of MDD with a high risk of suicide [19]: the WHO estimated that 1 million people die each year from suicide, of which more than 90,000 suffered from mental disorders (especially depression and substance abuse) [20].

MDD constitutes a heavy economic burden for society due to direct costs of the illness and workplace costs [21-28]. For instance, in the U.S., a 21.5% increased economic burden of MDD patients was estimated between 2005 to 2010, of which 45% due to direct costs, 5% due to suicide-related costs, and 50% due to workplace costs [29]. Despite the heavy burden and high prevalence of MDD, the percentage of MDD patients seeking treatment is relatively low: it has been estimated that 28-60% of depressed people actually receive or seek help [30, 31]. Up to 65% of people with severe depression symptoms have been reported not to get any treatment from a mental health professional [32].

Based on the above described numbers and facts about MDD, it is not hard to understand that unipolar depression is expected to be one of the leading causes of disability in the future [33-35]. Although many research efforts have been made to counter this development, getting better insight into the involved mechanisms and finding more effective treatments for MDD has proven to be difficult, with both treatment studies and etiological research struggling to obtain replicable results [36-45].

Taken together, although the massive global health consequences of depression have been acknowledged, complete knowledge about the underlying mechanisms and truly effective treatments are yet to be attained. One of the main reasons for this unfortunate state of affairs is considered to lie in the definition of MDD. Two aspects of the currently-used MDD classification have been criticized in particular: (i) it treats depression as a categorical syndrome (i.e. as a distinct
entity) rather than a continuous entity; and (ii) it allows for high levels of heterogeneity. Below, these two aspects are further elaborated on.

**MDD: a continuous or discontinuous entity?**

A basic assumption underlying the current depression classification is that mental health is a discontinuous phenomenon [46, 47]. The most commonly used diagnostic system, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 [48]) uses a syndrome-approach, where a “point of rarity” is assumed to exist between psychiatrically ill and healthy individuals [46]. This assumption stems from essentialism [49, 50] where “diseases are defined by a specific set of properties that are both necessary and sufficient for a diagnosis” [51]. Without a doubt, such a clear distinction enhances communications between patients, clinicians, scientists, insurance companies and institutions like the Ministry of Health and Welfare or the Food and Drug Administration. However, a clear cut-off between depressed and healthy individuals has never been observed in reality [47, 52-55]. Rather, studies have consistently shown that interpersonal depression variations in population samples are best captured by using a continuous spectrum where quantitative severity differences are used, rather than clear-cut ill vs. healthy qualifications [56-59]. Within such a ‘dimensional’ framework, all individuals can be seen as being located somewhere on a depression severity continuum, with healthy, non-depressed people being located at the one extreme (‘healthy’) end, those with varying (subclinical) levels of symptomatology being located along the spectrum in order of increasing severity, and severe MDD patients being located on the other extreme (‘severely pathological’) end [60, 61].

If this is the actual nature of depression, using a discrete cut-off point to classify depression leads to an artificial situation where all that do not meet the diagnostic criteria are assumed to have no mental problems at all. However, patients that do not meet DSM-criteria completely but have sub-threshold symptomatology have been shown to have clinically relevant problems even though they fail to meet all diagnostic criteria [62- 64]. These individuals remain untreated due to the absence of MDD diagnosis, although sub-threshold depression is associated with significant costs, disability, later development of MDD and suicide attempts [64, 65]. The discrepancy between the actual continuous nature of depression and the dichotomous operationalization that is used to classify it in research and clinical practice is problematic. In clinical practice, not all individuals with a need for help are identified, leaving opportunities for early detection of MDD development and the administration of minor but helpful preventive interventions unused [66, 67]. In research, using classifications that have an insufficient empirical basis and/or support is clearly suboptimal.
As there is no clear cut-off point between healthy and mentally-ill individuals, different dimensional models have been proposed to describe the symptomatology of mental illness. When looking at depression only, depressive symptom severity can be seen as a single continuum, along which all subjects in the general population can be aligned [68]. In the broader dimensional framework, the depression continuum is part of a larger set of psychiatric continua, which together form a multidimensional psychopathology construct [69-71]. Proponents of the dimensional view have argued that a dimensional approach simplifies diagnostics because only a limited number of dimensional scores are needed to distinguish between individuals instead of all the categories and specifiers for mood disorders that have been added in the successive editions of the DSM and have resulted in an unnecessarily complex diagnostic system. A particular problem of the DSM classifications is that the imposed boundaries between disorders are rather arbitrary and cause high levels of (artificial) comorbidity [72]. Here as well, a dimensional approach of depression has been argued to provide a solution. Dimensional models, such as the influential ‘Tripartite’ model [73] describe individuals by their scores on general and specific symptom dimensions instead of by a range of diagnostic labels, which has been shown to be useful in explaining high comorbidity rates between certain groups of mental disorders [73] but also in etiological research (e.g. [74]). The usefulness of the dimensional approach to describing and distinguishing between patients with comorbid depression and anxiety disorders [73] proves that it is important to focus on symptoms instead of only on syndromes [75].

To understand depression, the continuous construct of time also plays an important role. Research using multiple repeated severity assessments has shown that the vast majority of patients show course-trajectories that are characterized by gradual, continuous change over time (e.g. [76]). However, in psychiatric classification the course of depressive disorders is commonly described in terms that are based on dichotomous cut-offs, such as ‘remission’, ‘recovery’, ‘relapse’ and ‘recurrence’ [77]. The dichotomous nature not only plays a role in determining when mental problems are considered absent or present, they also play a role in describing the disorder’s temporal development. For instance, According to the DSM, there is a separation between remission and recovery at the 2-month mark: recovery indicates no substantial depressive symptoms for less than 2 months while recovery indicates no substantial depressive symptoms for more than 2 months [48]. Similarly, chronic depression is defined as meeting the MDD criteria for at least 2 years [48]. However, these temporal cut-off points are not empirically based and/or supported [78, 79] and the used time-intervals for recovery or remission may differ between different measures of depression severity [80].
Chapter 1 | Introduction

Taken together, the above shows that depression can be seen as continuous rather than discontinuous at three levels of the construct, namely, (1) in the inter-individual differences between patients, (2) in the way symptoms are best operationalized, and (3) in patterns of change over time. The content of this thesis aligns with this point of view about the MDD construct: continuity on the patient-, symptom- and time-level is assumed.

The heterogeneity of MDD

There are two major classification systems in which a definition is given of MDD: the DSM-5 [48] (Box 1) and the International Classification of Diseases, Tenth Edition (ICD-10 [81]). Patients identified with MDD under these diagnostic criteria are known to be highly heterogeneous, which hampers research and optimal treatment assignment in clinics. In line with the previous paragraphs, the issue of heterogeneity will be described in more detail for the patient level, symptom level, and time level of MDD.

Heterogeneity on the person-level

MDD patients can differ strongly from each other in several respects. MDD patients are diverse in terms of their symptom-patterns, severity-levels, age of onset, and the involved underlying causes and mechanisms [82, 83]. In addition, comorbidity rates are high among MDD patients, with prevalence rates of comorbid MDD and anxiety disorders reported to be 40-60% [84, 85]. This makes the number of possible variations among MDD patients even larger. Studies have identified several of the risk factors that can vary across MDD patients, including family history of MDD [86, 87], socioeconomic status [88-91] or gender [92-94]. Although depression rates are similar between boys and girls, these rates change drastically after puberty where the prevalence rate of women are 2-3 times higher than in men [95]. However, our understanding of the mechanisms that may determine such differences is still limited.

One area where the heterogeneity among MDD patients becomes particularly clear is daily clinical practice, where patients differ strongly with regard to their treatment response. The effect sizes found in treatment studies of antidepressants are usually close to 0.3 [96-98], which indicates that about 40% of MDD patients do not benefit more from antidepressants than from placebo [99]. In addition, some patients may struggle with side-effects, such as nausea or sleep disturbance, whereas others have limited side effects [100-101]. Unfortunately, side-effects are typically not well-described in published studies and generally under-studied, making it difficult for clinicians to judge beforehand if a patient might be at risk
of side-effects [102]. Several patient-characteristics, such as baseline severity and gender, have been found to be associated with treatment-response [97, 103, 104], but the optimal treatment-assignment strategy is still to be found.

<table>
<thead>
<tr>
<th>A.</th>
<th>Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms in either (1) depressed mood or (2) loss of interest or pleasure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).</td>
</tr>
<tr>
<td>2.</td>
<td>Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).</td>
</tr>
<tr>
<td>3.</td>
<td>Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.</td>
</tr>
<tr>
<td>4.</td>
<td>Insomnia or hypersomnia nearly every day.</td>
</tr>
<tr>
<td>5.</td>
<td>Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).</td>
</tr>
<tr>
<td>6.</td>
<td>Fatigue or loss of energy nearly every day.</td>
</tr>
<tr>
<td>7.</td>
<td>Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).</td>
</tr>
<tr>
<td>8.</td>
<td>Diminished ability to think or concentrate, or indecisiveness nearly every day (either by subjective account or as observed by others).</td>
</tr>
<tr>
<td>9.</td>
<td>Recent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicidal attempt or a special plan for committing suicide.</td>
</tr>
</tbody>
</table>

| B. | The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. |
| C. | The episode is not attributable to the physiological effects of a substance or to another medical condition. |
| D. | The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and psychotic disorders. |
| E. | There has never been a manic episode or a hypomanic episode. |

**Box 1: Diagnostic Criteria for Major Depressive Disorder (DSM-V[48])**

**Heterogeneity on the symptom-level**

As shown in Box 1, DSM-5 defines MDD to be present if 5 out of 9 listed criteria are satisfied, with at least one of 2 core symptoms (depressive mood and loss of interest) being present. This so-called syndrome approach is based on the summing of symptoms and rests on the assumption that depressive symptoms are interchangeable. However, empirical studies have showed otherwise [51, 75, 105]. Moreover, the selection of 5 out of 9 symptoms with 1 or 2 core symptoms allows for 227 possible symptom combinations to be diagnosed as MDD. Thus, in theory
the same diagnosis can entail rather different symptom patterns. Indeed, researchers using a depression severity measure consisting of 12 symptoms in a large sample of depressed outpatients (N=3,703), found 1,030 unique symptom profiles, of which even the most common symptom profile was observed only in 1.8% of the patients [106].

**Heterogeneity on the time-level**

Temporal heterogeneity is non-negligible when we consider the course of depression. Different patients follow different course-trajectories over time and different symptoms may follow distinct trajectories within a single patient. The current diagnostic standard provides little means to distinguish between these different temporal patterns. Cut-offs have been introduced to facilitate the formulation of treatment strategies and/or the communication between clinicians or researchers. As described above, the DSM-5 uses a cut-off point of 2 months to define different states (i.e. remission or recovery) in the course of MDD. However, such a clear cut-off point is not supported by empirical evidence [76, 78, 107]. Rather, the course of depressive symptomatology over time has a more dimensional nature. Therefore, when trying to capture variations in course over time it may be helpful to model (growth on or change in) latent dimensions to represent the time heterogeneity and/or certain states in the MDD course (e.g. recovery).

**Subtypes of MDD**

The problem of MDD heterogeneity has been identified as a major obstacle for MDD research [108]. Therefore, many studies have been conducted to identify more homogeneous MDD subtypes, hoping that such subtypes would lead us to more specific clinical presentations and its etiology. To this end, mainly two approaches have been taken: (1) to identify sub-categories based on clinical insights and (2) to identify data-driven subtypes.

In the first, clinically-based approach, more homogeneous subtypes were defined based on clinical observations about, for instance, time of onset, particular symptom profiles and/or supposed underlying causes. Currently, the DSM-5 distinguishes between clinical subtypes of MDD, based on the onset of MDD (seasonal affective disorder, postpartum depression), the severity of MDD (catatonic depression) or particular combinations of symptoms (melancholic depression, atypical depression) [48]. Indeed, some emphasized clinical characteristics, such as hypersensitivity and changing mood in atypical depression, have been observed [109, 110]. In addition, it has been suggested that patients with atypical MDD benefit comparatively strongly from treatment with MAO-
the same diagnosis can entail rather different symptom patterns. Indeed, researchers using a depression severity measure consisting of 12 symptoms in a large sample of depressed outpatients (N=3,703), found 1,030 unique symptom profiles, of which even the most common symptom profile was observed only in 1.8% of the patients [106].

Heterogeneity on the time-level

Temporal heterogeneity is non-negligible when we consider the course of depression. Different patients follow different course-trajectories over time and different symptoms may follow distinct trajectories within a single patient. The current diagnostic standard provides little means to distinguish between these different temporal patterns. Cut-offs have been introduced to facilitate the formulation of treatment strategies and/or the communication between clinicians or researchers. As described above, the DSM-5 uses a cut-off point of 2 months to define different states (i.e. remission or recovery). However, such a clear cut-off point is not supported by empirical evidence [76, 78, 107]. Rather, the course of depressive symptomatology over time has a more dimensional nature. Therefore, when trying to capture variations in course over time it may be helpful to model (growth on or change in) latent dimensions to represent the time heterogeneity and/or certain states in the MDD course (e.g. recovery).

Subtypes of MDD

The problem of MDD heterogeneity has been identified as a major obstacle for MDD research [108]. Therefore, many studies have been conducted to identify more homogeneous MDD subtypes, hoping that such subtypes would lead us to more specific clinical presentations and its etiology. To this end, mainly two approaches have been taken: (1) to identify sub-categories based on clinical insights and (2) to identify data-driven subtypes.

In the first, clinically-based approach, more homogeneous subtypes were defined based on clinical observations about, for instance, time of onset, particular symptom profiles and/or supposed underlying causes. Currently, the DSM-5 distinguishes between clinical subtypes of MDD, based on the onset of MDD (seasonal affective disorder, postpartum depression), the severity of MDD (catatonic depression) or particular combinations of symptoms (melancholic depression, atypical depression) [48]. Indeed, some emphasized clinical characteristics, such as hypersensitivity and changing mood in atypical depression, have been observed [109, 110]. In addition, it has been suggested that patients with atypical MDD benefit comparatively strongly from treatment with MAO inhibitors [111]. However, the utility of subtypes has been the subject of ongoing discussions [72] and etiological studies based on such subtypes have not led to conclusive findings [112, 113].

A bottom-up, data-driven approach is an alternative way to identify more homogeneous subtypes. In this type of research, cluster techniques such as Latent Class Analysis (LCA), Factor Analysis (FA) and Principal Component Analysis (PCA) are used to identify groups and/or clusters based on data-driven algorithms. Such an approach can be used to assess heterogeneity at different levels of the depression phenotype. For instance, factor analysis can be used to gain insight into the heterogeneity of symptoms [114] and LCA can be used to identify more homogeneous subgroups of patients [115-117]. To gain a good overview of the different levels of heterogeneity and the way they are connected to each other, it is useful to represent the data as a cubic object [118] or three-way array [119, 120] (Figure 1A). Such a cubic dataset consists of S symptom scores, or measured data (s-axis) for P persons (p-axis) at T time points (t-axis). For all longitudinal datasets, where the same symptoms are repeatedly assessed in the same group of subjects, the data can be arranged in this format. The resulting data cube can be analyzed in three directions, taking either a horizontal, lateral, or frontal slice (Figure 2). Different statistical models are available to investigate heterogeneity in each of these slices. Below, a summary is given of these methods.
Figure 1 (A) Cattell’s ‘data-cube’, (B) latent class analysis with three classes (red, green, blue) in the P x S slice, (C) factor analysis with two factors within the P x S slice, (D) growth mixture analysis with three classes (red, green, blue) within the P x T slice. Figure reprinted from “Diagnostic heterogeneity in psychiatry: towards an empirical solution”, Wardenaar KJ, de Jonge P [121] with permission.

Figure 2. A cubic data, cut into slices
To analyze heterogeneity in the frontal slice (i.e. the P-by-S slice), LCA has been used to identify MDD person subtypes based on variations in their associated symptom patterns (Figure 1B) [115, 122-124]. Conversely, FA or PCA has been used to identify symptom subdomains based on their correlations (i.e. co-occurrence) in a dataset (Figure 1C) [114]. Although applied to the frontal slice, it is important to note that the described techniques approach the data from different directions, with LCA tackling heterogeneity on the person-level and FA/PCA tackling heterogeneity on the symptom-level. To analyze a lateral slice (i.e. the P-by-T slice), growth mixture analyses (GMA) have been used to find course-trajectory classes with different temporal trajectories on one or more repeatedly measured variables (Figure 1D)[76, 125-136]. For the analysis of the horizontal slice (i.e. the S-by-T slice), time-series analyses have been used (with or without the additional use of network analyses [137, 138]) to gain insight into within-person dynamics of single symptoms or symptom dimensions over time (e.g. [139]). Although the use of each of the above described techniques has offered useful insights into the various sources of depression heterogeneity [58, 140], each of the approaches only tackles heterogeneity in one slice at a time. None of the models incorporate and explain all three sources of heterogeneity (persons, symptoms and time) in one model, although it is likely that important interactions between the different levels are overlooked in this way [114, 141].

Addressing three sources of heterogeneity in one model has been attempted in different ways: using either a latent variable approach or a network approach. These approaches postulate different assumptions about the concepts of psychopathology. The former approach follows the traditional view on psychopathology that latent constructs (i.e. classes or dimensions) exist and underlie or cause the observed symptoms. More specifically, in this conceptualization of psychopathology, it is assumed that depression heterogeneity on the person-, symptom- and time-level can be explained by underlying, more homogeneous latent constructs. Conversely, the network approach assumes that there is no latent structure. Rather, observed depression symptoms are seen as nodes in a network of causally connected symptoms [142]. Recently, this approach has been increasingly applied to depression data [143-146] with mixed results. It has been hypothesized that higher levels of psychopathology are associated with more densely connected networks, but this has not always been supported by evidence [147]. Furthermore, the network approach is often used in attempts to describe within-person symptom dynamics (e.g. symptom A led to symptom B, which led to symptom C etc.). When used in this way, the network approach essentially focuses on what happens with a single person in an ‘N=1’ fashion, which means that each other person is regarded as a new replication.
Chapter 1 | Introduction

Because of this strong assumption, such a network approach does not allow for a direct quantitative evaluation of heterogeneity at the person-level [147].

Given the above, the current thesis aimed to evaluate the use and usefulness of a latent variable approach that addresses the three major sources of depression heterogeneity and their interactions in a single model, while doing justice to the continuous nature of depression. To this end, an approach called Three-mode Principal Component Analysis (3MPCA [148, 149], or Tucker 3 [150] analysis or Three-mode factor analysis [119, 120]) was used and evaluated in different datasets. 3MPCA is a multi-way version of regular PCA, which has been frequently used to explore the heterogeneity of depression symptomatology. 3MPCA works in a similar way, but can be used to summarize person-, symptom- and time-level heterogeneity with a small number of components for each of the three entities as well as their interactions. Although this approach has been applied in other fields, such as chemistry and psychology, it has hardly been applied in MDD research [121, 151].

Overview of this thesis

In the current dissertation, the heterogeneity of depression regarding the three different sources is studied in an overarching way by means of 3MPCA. First, a more traditional growth mixture approach is used to model MDD heterogeneity by considering the course of patients on two symptom-domains (Chapter 2). Second, the same dataset is analyzed with 3MPCA, incorporating three sources of heterogeneity (patients, symptoms and time) in one model (Chapter 3). The resulting components are further evaluated in terms of their clinical value. More specifically, the long-term prognostic value of the resulting 3MPCA components is compared with those of known predictors and solutions from other statistical models (Chapter 4). In the second half of the dissertation, 3MPCA is used to obtain better insight into the heterogeneity on antidepressant treatment response and/or outcomes (Chapter 5) and into patterns of comorbidity (Chapter 6). Finally, the main findings are summarized and their methodological and clinical and implications are discussed (Chapter 7).
Introduction | Chapter 1

References

Chapter 1  | Introduction


Chapter 1 | Introduction

51. Fried EI. Problematic assumptions have slowed down depression research: why symptoms, not syndromes are the way forward. Frontiers in psychology. 2015 Mar 23;6:309.
75. Fried EI, Nesse RM. Depression sum-scores don’t add up: why analyzing specific depression symptoms is essential. BMC medicine. 2015 Apr 6;13(1):1.
Chapter 1 | Introduction

76. Wardenaar KJ, Conradi HJ, Jonge P. DATA-DRIVEN COURSE TRAJECTORIES IN PRIMARY CARE PATIENTS WITH MAJOR DEPRESSIVE DISORDER. Depression and anxiety. 2014 Sep 1;31(9):778-86.
90. Gallo LC, Matthews KA. Understanding the association between socioeconomic status and physical health: do negative emotions play a role?. Psychological bulletin. 2003 Jan;129(1):10.
Chapter 1 | Introduction

105. Fried EI, Nesse RM, Zivin K, Guille C, Sen S. Depression is more than the sum score of its parts: individual DSM symptoms have different risk factors. Psychological medicine. 2014 Jul 1;44(10):2067-76.


Chapter 2
Symptom-specific course trajectories and their determinants in primary care patients with Major Depressive Disorder: Evidence for two etiologically distinct prototypes
Klaas J. Wardenaar
Rei Monden
Henk-Jan Conradi
Peter de Jonge
Journal of Affective Disorders
2015 Jul 1; 179:38-46

*pm 2:51* (Painted by Miho Hashimoto)