Chapter 1

Introduction

Preface

Suffering is an integral component of the human condition. Nothing in life is permanent, and since even the happiest of moments must come to an end at some point, loss is unavoidable. None of us are exempt from negative emotions like fear, sadness, and grief. Fortunately, these emotional states generally are impermanent as well. As we recover from whatever experience life throws at us, the negative emotions will pass. However, this kind of emotional resilience seems to come more difficult to some people. Through the ages, a certain percentage of the population has been affected by unusually prolonged states of depressed mood - a condition which the ancient Greeks called melancholia.[1,2] It is important to note that feeling melancholic or depressed is not necessarily a sign of pathology or mental illness. These days it is not unusual to hear someone say the news was really depressing in a casual conversation, or that they have been depressed after a recent break-up.

Major Depression

It is difficult to determine exactly where normal variation in mood ends and pathology starts.[3,4] Since there is a continuum of severity and pervasiveness from ordinary sadness to clinical depression, it makes sense for the boundary to be fixed on pragmatic grounds, i.e., giving priority to clinical utility.[5] This is what the American Psychiatric Association (APA) attempts to achieve in their Diagnostic and Statistical Manual of Mental Disorders (DSM), regarding depression as a 'disorder' when it reaches a given threshold in terms of severity, duration and degree of suffering or functional impairment (see Box 1, criterion B), thus deserving clinical attention.[6] The quality of life is often low for people diagnosed with MD, because MD impacts all aspects of a person's life, limiting their ability to function at work and manage daily tasks like cleaning and shopping, and slowly spoiling their social lives and close relationships.[7,8] Indeed, MD is experienced as more disabling than even many physical disorders such as chronic pain, heart disease or even cancer.[9–11] MD is currently the single largest contributor to the global burden of disease, and MD patients are most likely to commit suicide of all patients diagnosed with mental disorders (see Box 2 for some more key figures).[12–14] Currently, Dutch patients presenting with MD at their general practitioner's (GP) office receive problem solving treatment (PST) or guided self-help interventions, or, if their symptoms are too severe, they are referred to a specialist for psychotherapeutic interventions such as cognitive-behavioral therapy (CBT)

or interpersonal psychotherapy (IPT).[15] If the patient does not want psychotherapy or the therapy is not effective enough, the GP can also offer antidepressant medication such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCA).[15]

Box 1. Major Depression - diagnostic criteria according to the DSM-5[6]

A. 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 is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. 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). (Note: In children and adolescents, can be irritable mood.)
2. 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).
3. 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. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear dying), recurrent suicidal ideation without a specific plan, or suicide attempt or specific plan for committing suicide.

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.

Note: Criteria A-C represent a major depressive episode.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in criteria a, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of major depressive episode in addition to normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on individual's history and cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by seasonal affective disorder, schizophrenia, schizophrenic form disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or hypomanic episode.

Note: This exclusion does not apply if all the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Unfortunately, most MD treatments are associated with moderate effect sizes (see Box 2). Better understanding of patient-specific causal mechanisms is expected to facilitate the development of biologically informed, patient-specific diagnoses, which in turn should enable psychiatrists to provide treatments that are tailored to a patients' etiological and pathophysiological background.[16,17]

Box 2. Major Depression - key figures

MD is:
- the second most common mental disorder in the world[18,19]
- the single largest contributor to the global burden of disease[12]

Worldwide:
- 300 to 350 million people suffer from MD[20-22]
- 1 in 5 people will experience MD in their lifetime[23-25]
- Women suffer from MD roughly twice as often as men[20,26,27]

MD is highly comorbid with:
- anxiety disorders (50-60%, lifetime)[28]
- substance use disorder (30-40%, lifetime SUD among treatment-seeking MD patients)[29]
- coronary heart disease (80% higher chance)[30]
- overweight and diabetes (40-60% higher chance)[31-33]

Death by suicide:
- affects 800,000 people every year[34,35]
- involves a mood disorder in 43-59% of cases[36,37]

Of all MD patients:
- about 50-70% recover within a year[38]
- about 20% develop a chronic course[39,40]
- about 30-60% seek treatment.[41]

Based on meta-analyses, treatment effect sizes are:
- 0.34-0.40 for PST (Cohen's *d*)[42,43]
- 0.22 for CBT (Hedge's g, Cohen's *d*)[44,45]
- 0.60 for IPT (Hedge's *g*)[46]
- 0.32 for SSRIs/SNRIs (Hedge's *g*)[47]
- 0.42 for TCAs (Cohen's *d*)[48]

CBT, cognitive-behavioral therapy; IPT, interpersonal therapy; MD, Major Depression; PST, problem-solving therapy; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SUD, Substance abuse disorder; TCA, tricyclic antidepressant

Causes of MD

Throughout history, theories about what exactly ails depressed people have varied widely, ranging from ideas about an excess of black bile to a theories about a conflict between the id and the superego.[1,2] Today, we recognize that MD is an exceedingly complex multifactorial disorder, involving a wide range of interacting risk factors from different levels (see Figure 1).[49–51] According to the diathesis-stress model, MD is not caused by one biological or psychological factor in isolation.[51,52] Rather, in a vulnerable patient, who is predisposed to a negative response to stress, repeated stressors can cause that pre-existing vulnerability (i.e., diathesis) to manifest itself.

This development from pre-existing vulnerability to full-blown MD can be investigated at different levels (see Figure 1). At the phenotypic level, MD includes symptoms like depressive affect, feelings of worthlessness, motor symptoms, and suicidal ideation. However, these symptoms do not arise in all patients. Box 1 shows that there are many different symptom profiles that could fit the diagnostic classification of MD. A number of the additional symptom criteria of MD concern changes (either an increase or a decrease) in appetite, weight, amount of sleep, amount of motor activity, and arousal, which means that some MD patients may have almost opposite symptom profiles. For example, one patient may suffer from weight loss, insomnia, and psychomotor agitation where another patient is plagued by weight gain, hypersomnia, and psychomotor retardation. Most of these symptom profiles are shared by a small percentage of the population only.[54] Other sources of heterogeneity on the clinical level are the severity and course of the disorder. For example, the duration of episodes varies. Based on 15 years of clinical observations, the US National Institute of Mental Health estimates that 67% of patients recover within a year.[55] The recovery is estimated to be 88% after 5 years, and 93% by 10 years.[55] A more recent study in the general population supports these findings, showing that about 50% of new MD patients recover without further episodes, but there is also a sizeable portion (~35%) that experiences recurrent episodes, and about 15% of patients suffer from a chronic course.[56] It should be pointed out that phenotypical heterogeneity by itself is no cause for concern, since this phenomenon also occurs in many somatic disorders.[57,58] However, because the heterogeneity of MD extends to the pathophysiological and etiological levels, identifying the pathophysiological processes leading to this disorder has proven to be more difficult.[49,59,60]

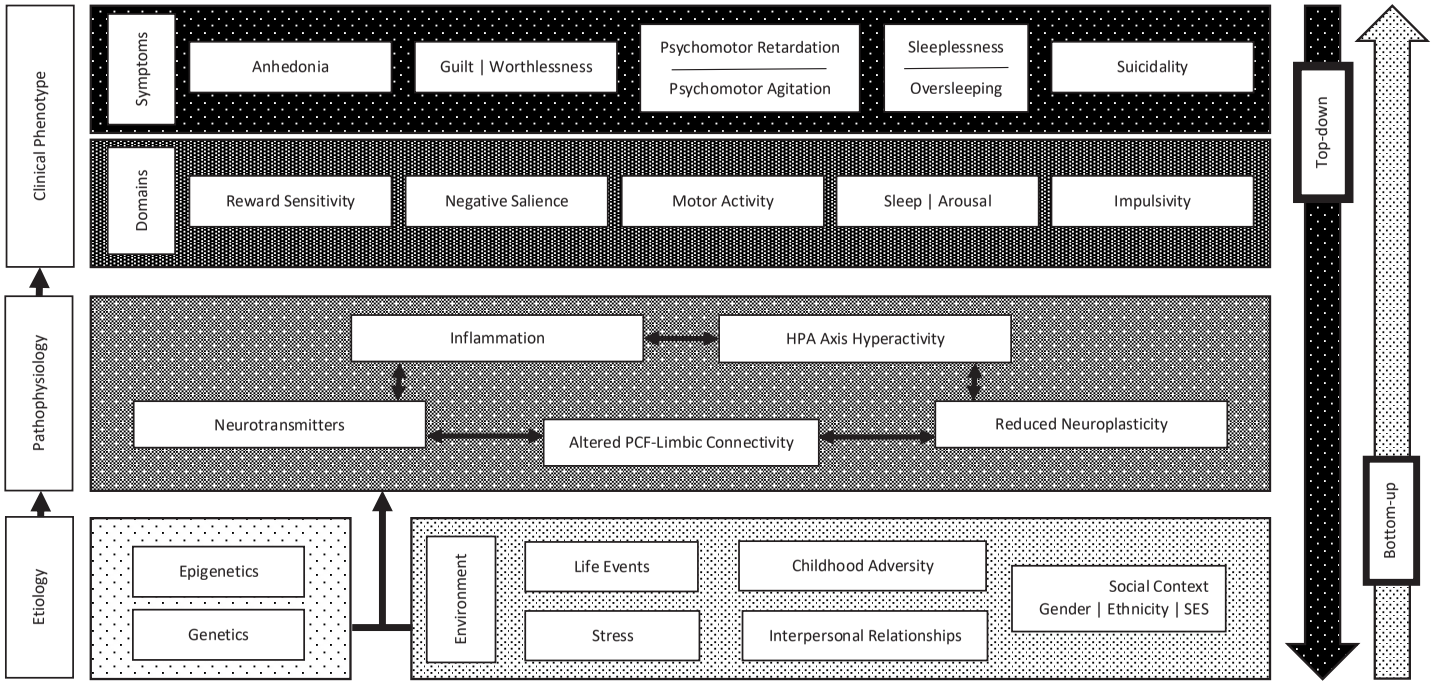

Figure 1. A unified theory of depression

Numerous genetic and environmental etiological factors interact to cause one or more reciprocally interactive pathophysiological mechanisms, which in turn cause symptomatic phenotypic expression, organized here according to domains from the Research Domain Criteria[53]. Adapted from "The neurobiology of depression: An integrated view" by Dean & Keshavan (2017), with permission.

At the pathophysiological level, the putative underlying mechanisms of MD can be organized according to different categories like neurochemistry[61], tissue- and organ-level pathology (e.g., inflammation[62] or an increased stress response[63]), and altered neurocircuitry[64,65].[59] The most commonly prescribed medication (i.e., SSRIs/TCAs) is based on the proposition that MD is a result of diminished activity of serotonin pathways (i.e., the serotonin hypothesis) or both serotonin and catecholamine pathways (i.e., the monoamine hypothesis).[66–68] However, there are some problems with these hypotheses, chief among which is the modest effect size of antidepressant medication[47,48], which suggests that either these drugs do not actually increase serotonin levels, or that many of the people currently taking SSRIs might not have dysfunctional serotonin pathways in the first place.[47,69] The latter seems more likely, because although a transient lowering in brain serotonin activity can be induced in multiple ways, this has failed to induce depression in healthy subjects like it does in people with a history of MD.[68] Furthermore, it has been shown that some MD patients have lower monoamine levels, but there are also patients with similar levels compared to healthy controls.[70–73] Treatments based on other theories suffer from similar issues. For example, the effect size of anti-inflammatory treatments for MD is estimated to be about 0.34-0.55 (Cohen's *d*) on average, but research suggests that this might be the result of averaging over patients with and without immunological dysregulations.[74–79] It is important to note that it is often difficult to tell whether the biological differences between MD patients and controls are really part of the pathophysiology of the disorder. They could also be a result of psychopathology-induced lifestyle changes, or they might be better categorized part of the etiology of the disorder, because they are a result of a genetic predisposition.

At the etiological level, the predisposition to a negative response to stress is thought to be a result of genetic[80,81] and epigenetic factors related to the pathophysiological mechanisms mentioned above[82,83], interacting with environmental factors such as traumatic life experiences[84,85] or socioeconomic status[86]. None of these factors are by themselves sufficient to cause MD, and none of them are absolutely required for the development of the disorder.[87] Indeed, the correlations between single risk factors and the presence of MD tend to be weak, which could mean that the total risk of MD consists of many small effects.[88,89] It could also be that each risk factor is more strongly related to the development of MD for some patients and less so in others, which would result in a low average observed correlation in the complete patient group.[90–92]

Overall, this evidence suggests that there is not one biological disturbance underlying depression in all patients (i.e., impaired serotonin functioning) that underlies MD in all patients, which can be targeted with one type of treatment.[67,93,94]

Investigating the etiology of MD

Since the effectiveness of current therapies relative to placebo is modest other approaches are necessary to address the public health burden of MD.[47,69,95] Preventive interventions for both first onsets and recurrent episodes of MD seem like a promising avenue.[96,97] Identifying key risk factors for MD will help us provide focal points for preventive interventions.[96–98] As described above, potential risk factors for MD range from genetic and environmental variables to different types of biological disturbances.[49]

One method to identify key risk factors for MD is relative importance analysis, which calculates the proportion explained variance of each variable, by comparing the statistical fit of all possible models that include the variable in question to that of the complete collection of possible models.[99,100] This means that putative risk factors should be investigated together in a large general population study. Unfortunately, studies that would enable such analyses are rare, because collecting data on a large group of variables in a sizeable group of participants is expensive and time-consuming. Almost all longitudinal general population studies investigating onset and/or recurrence of MD include either: (a) a sample with a limited age range, (b) only males or females, (c) a limited sample size or (d) a limited number of risk factors.[101–112] Furthermore, the computational power required of this type of analysis is large, and increases exponentially with each additional variable. Therefore, most studies report models including individual risk factors instead, or opt to specify a single multivariable model including all variables that are significant in univariable analyses.[56,113,114]

Other limitations of commonly used models include their inability to investigate patterns more complex than a u-curve. Linear regression models suffice to study general trends, but these models are unable to accommodate different patterns.[115] For example, it is common knowledge that women suffer from depression more often than men, but how exactly MD varies across age and sex has been subject of debate for a long time.[115–117] More insight into these patterns could be used to improve opportunities for public health interventions by identifying sub-populations with higher MD prevalence or incidence because of specific life phases, such as parenthood or menopause.[117–119]

The heterogeneity of Major Depression

Elucidating the etiology of MD is complicated further by the heterogeneity of the patient population. Good classifications group individual in such a way that all the members have roughly the same chance for some relevant characteristic or outcome, i.e., the intra-class homogeneity should be high.[120] When it comes to MD, this means that in the ideal scenario, patients share similar genetic or environmental risk factors, similar pathophysiology, and respond well to similar specific treatments like SSRIs or CBT. Ideally, there is also high inter-class heterogeneity, meaning these characteristics should vary widely between MD and other classes like Generalized Anxiety Disorder (GAD).[120] If that is the case, class membership can be established with high certainty, and optimal treatment for an individual patient can be determined by referring back to the classification.[120] One way to improve the intra-class homogeneity of the MD diagnosis is to look for more homogeneous groups within the population of patients diagnosed with MD (i.e., subtypes). The first clinical subtypes of MD were largely based on clinical consensus, not unlike the MD classification itself.[121] Unfortunately, clinical subtypes of MD have not performed much better with regards to prediction of onset, course, and treatment response than the original MD classification.[122]

Data-driven subtyping of Major Depression

Data-driven approaches address the issue of intra-class heterogeneity by using computational methods to identify patterns in data, which might have been missed by clinical observeration.[123] Although data-driven approaches to psychiatric diagnostics have long been used in psychiatric research, they have recently gained more popularity.[123–132] This is likely a result of the growing realization that better-specified phenotypes are needed, but also due to the increasing availability of suitable datasets and ongoing advances in statistics and machine learning.[123,133,134] However, because of several methodological issues, it is still unclear how much of an improvement can be made with data-driven subtypes.

The influence of methodological variation

Data-driven subtyping is usually performed using some form of unsupervised learning (i.e., finite mixture models and clustering algorithms such as k-means clustering, hierarchical clustering, and community detection[123]). Whereas supervised learning either succeeds at predicting a predefined outcome (e.g., onset of MD, treatment response, chronic course)

or not, unsupervised learning aims to detect previously hidden structures in data, which means there is no straightforward way to judge the quality of unsupervised learning results. Because of this, there is a plethora of different unsupervised learning methods, and the amount of different model specifications available is a lot larger compared to supervised learning.[135] This means that, since the specifics of a chosen analytical method can have a significant influence on research outcomes, variations across studies are a realistic risk when it comes to unsupervised learning algorithms.[136–138] And while a statistical model is not necessarily valid just because it is robust to methodological variation, significant changes to the model as a result of a different set of methodological decisions leads to serious doubts about its validity.[139] Thus, increased insight into the effects of methodological variation on unsupervised clustering results could help us prevent overinterpretation of the results from our data-driven subtyping models. In addition, it could provide leads for data-driven subtypes of MD by identification of patterns that are robust to methodological variation.

Top-down vs. bottom-up

It is also unknown which type of data will deliver the best results when it comes to data-driven subtyping. Even though cluster algorithms do not prioritize any explanatory level over the other *a priori*, research into diagnostic subtypes of depression has thus far predominantly focused on subtyping based on higher-level data such as symptom patterns, comparing lower-level etiological and pathophysiological differences post-hoc (i.e., top-down subtyping, see Figure 1).[120,123,131] However, there is little evidence showing that heterogeneity in etiology and treatment response are best explained by variations at the level of symptoms, as data-driven subtype classifications based on cluster analyses of symptoms have been shown to have limited value when it comes to prediction of course and treatment response.[123,131,140] In fact, there is no obvious reason to assume that similar symptoms will always be caused by similar pathophysiology or similar etiology, as there are plenty of examples in medicine where different pathologies lead to similar symptoms and biomedical tests are required to differentiate between them (i.e., equifinality).[141] For example, a fever can be caused by some kind of viral or bacterial infection, by inflammatory conditions like rheumatoid arthritis, but also by a heat stroke.[142] Therefore, it would be very interesting to perform subtyping based on other sources of heterogeneity, including clinical risk factors, biochemical markers, genetic variations, and brain region activity/connectivity. Indeed, research initiatives such as Research Domain Criteria and large-scale projects, such as the Roadmap for Mental Health Research in Europe have emphasized the need to incorporate multiple levels when investigating psychiatric disorder mechanisms.[143–145]

Instead of using a top-down approach of comparing differences between higher-level symptom-based subtypes on lower explanatory levels such as pathophysiology or etiology, it might be worthwile to apply a bottom-up approach, starting with lower-level data and working our way up from there (see Figure 1). In this way, we might be able to identify groups of people that share a similar etiology and/or similar pathophysiology, which means there are more likely to respond to similar treatments. Symptom profiles might differ between these groups, or they might not – this is of lesser importance than predicting treatment response. Still, recent top-down subtypes might provide an interesting guide mark for bottom-up subtyping based on lower-level data. For example, Latent Class Analysis (LCA) resulted in one moderate and two severe depression subtypes in the Netherlands Study of Depression and Anxiety (NESDA).[146,147] The severe subtypes mainly differed on the probabilities of diurnal variation, early morning awakening, hypersomnia vs. insomnia, and increased vs. decreased appetite and weight. Subsequent studies showed that the subtype with increased weight and appetite had, among other things, higher leptin, insulin, and fatty-acid-binding protein scores, higher metabolic syndrome risk, and a higher probability of carrying a genetic variant of obesity-associated protein (FTO; rs9939609).[147–151] They also had higher inflammation marker levels (e.g., C-reactive protein, interleukin-6, complement C3).[151,152] If subtypes based on biomarkers such as the metabolic and inflammation-related markers mentioned above include similar patients as these top-down subtypes, this might imply that the differences in symptoms do, in this case, indeed reflect different pathologies.

This thesis

In summary, the MD classification captures a group of patients with a high burden of disease, but MD patients are a heterogeneous group in many ways, which constitutes a major challenge for research into the underlying etiological and pathophysiological processes, as well as the development of more effective, tailored. Based on this heterogeneity, it seems that theories stating that there is one biological disturbance underlying depression in all patients (i.e., impaired serotonin functioning) that underlies MD in all patients are unlikely to be valid. In fact, previous studies have identified many potential risk factors, but in order to figure out which of these are the most important for predicting MD onset and recurrence, they need to be investigated together in a large general population study, and understanding the relationship between specific risk factors such as age and sex requires more sophisticated non-linear models. Since it is possible that different risk

factors are more strongly related to the development of MD in some patients and less so in others, looking for subtypes of MD is another promising avenue for improving prevention and treatment efforts. However, bottom-up subtyping based on etiological or pathophysiological data is as of yet largely unexplored. The aims of this thesis are to gain more insight into the etiology of MD by (1) using rich datasets and novel methodology to take a more detailed look at MD risk factors and (2) to investigate if and how well bottom-up subtyping approaches might enable the discovery of more homogeneous subtypes of MD.

The first part of this thesis (Chapters 2-3) describes studies that use sophisticated statistical models in combination with a large and rich dataset to refine our understanding of the etiology of MD. In Chapter 2, relative importance analysis was used to investigate which risk factors are most important, using rich set of risk factors for the incidence and chronicity of MD in a large population study. In order to take a more detailed look at the relationship between sex, age, and internalizing psychopathology, the next study applied advanced non-linear modelling to a large population sample, investigating the prevalence of MD and other internalizing disorders as well as mean scores for internalizing symptoms and traits over the lifetime (Chapter 3).

The second part of this thesis (Chapter 4-6) focuses on methodological and empirical questions about bottom-up MD subtyping. Chapter 4 aimed to gain insight into existing knowledge about the role of biological factors in MD heterogeneity by means of a systematic review of current evidence available for data-driven biological subtypes of MD from studies that identified (1) data-driven subtypes of MD based on biological variables, or (2) data-driven subtypes based on clinical features such as symptom patterns and validated these with biological variables post-hoc. In order to investigate whether it was possible to successfully apply clustering techniques commonly used in studies based on clinical data to a set of biochemical biomarkers, Chapter 5 attempted to identify biochemical subtypes of MD using Latent Class Analysis. The final Chapter describes the use of Specification-Curve Analysis to gain more insight into the influence of methodological variation on biomarker-based cluster-analysis results (Chapter 6).

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