A sad day's night

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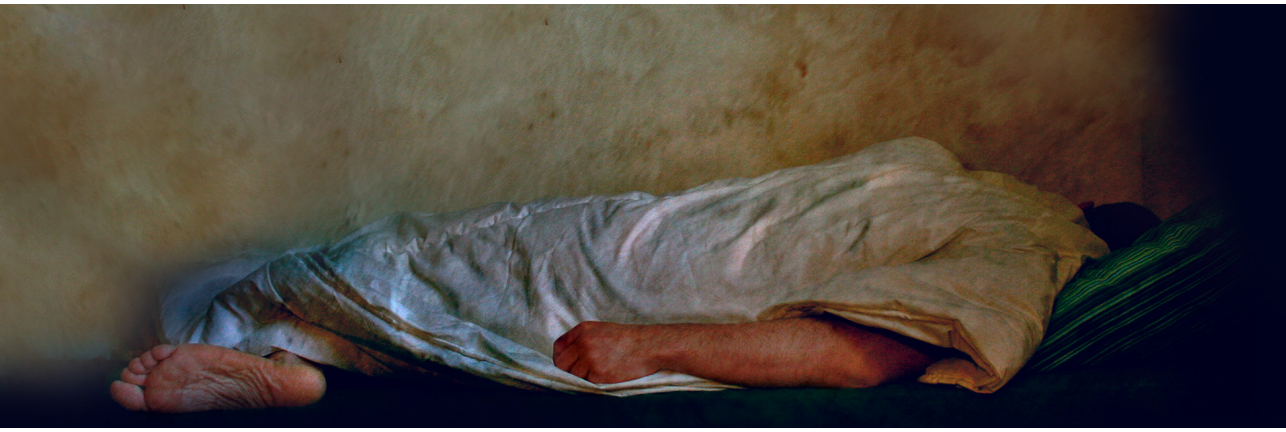
Chapter 1

General Introduction



Sleep Disturbances

Around 30% of the general population report having occasional sleep disturbances[1-3]. Sleep disturbances may involve having trouble initiating or maintaining sleep, waking up too early, or suffering from nonrestorative sleep[1,2]. Prevalence rates drop to around 18% in case the criterion applied is that the sleep disturbance has to be present for at least 3 nights a week. With the additional criterion that the sleep disturbance must cause clinically significant distress or impairment, prevalence rates drop to 10% of the general population[2]. Around 6% of the general population suffer from a diagnosis described in the Diagnostic and Statistical Manual 5th edition (DSM-V[4]) under the category Insomnia Disorder: one or more of the abovementioned symptoms for at least 3 nights a week in the last 3 months, which cause significant distress or impairment, and are not caused by other sleep or mental disorders or by substance use. The opposite of insomnia is commonly known as hypersomnia, which occurs in around 3% of the population. This disturbance refers to excessive sleepiness despite a main sleep period of at least 7 hours, either by recurrent daytime sleep episodes, by prolonged sleep episodes of > 9 hours per day, or by difficulty being fully awake after abrupt awakening. These symptoms must occur at least 3 times a week for at least 3 months, must cause clinically significant distress or impairment, and should not be caused by other sleep or mental disorders or by substance use to be diagnosed with the DSM-V category of Hypersomnolence Disorder[4]. Dissatisfaction with subjectively assessed sleep quality or quantity showed comparable prevalence rates as insomnia symptoms that occur at least 3 nights a week: around 19% of the general population reported dissatisfaction with sleep quality or quantity[1]. Sleep disturbances are closely related to impaired emotional and cognitive functioning[5] such as decreased emotional intelligence and declined constructive thinking skills[6]. Individuals with sleep disturbances are also more likely to report poorer health, and make greater use of healthcare[1]. In 40% of individuals with sleep disturbances their sleep disturbance co-occurs with a mental disorder[7], whereas only 16% of individuals without sleep disturbances suffer from a mental health disorder[1-3]. Most research on sleep disturbances and mental health disorders has been focused on Major Depressive Disorder (MDD). This is not surprising, because MDD is strongly associated with sleep disturbances[8]. Sleep disturbances are part of DSM-V MDD's diagnostic criteria[4] (Box 1) and are present in approximately 70% of MDD patients[8,9]. Next to that, sleep disturbances are known to be an underlying risk factor for developing MDD[3,10-12]. Suffering from insomnia doubles the risk to develop MDD[13]. Sleep disturbances often persist after remission of MDD. Around 40% of patients report sleep disturbances during periods of remission[9], and it is well-known that the presence of residual sleep disturbances increases the risk of recurrence of MDD[14].

Major Depressive Disorder

MDD is one of the most common and debilitating mental health disorders in the Western world[15]. Worldwide, MDD is ranked as the 4th leading cause of disability by the World Mental Health Organization, and it has been predicted to rise to the 2nd place by 2020[16]. Lifetime MDD prevalence rates range from 1 to 19% for different countries, with a twice as high lifetime risk to develop MDD for women compared to men. The course of MDD is often chronic-recurrent[16]. Up to 35% of MDD patients do not respond well to available treatment. Partial response, meaning 25-49% symptom reduction from baseline, occurs in around 15% of MDD patients. Conradi et al.[9] showed that MDD patients report on average two residual symptoms out of the nine DSM-V depressive symptoms during periods of remission, of which sleeping disturbances are present in around 40% of the occasions. Residual symptoms such as sleep disturbances have been associated with a 3.5 times higher risk of recurrence compared to patients that achieved full remission[17]. However, treatment until full remission is achieved is not common practice[9].

Box 1. *MDD symptoms according to DSM-V.*

(1)	Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others.
(2)	Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
(3)	Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.
(4)	Insomnia or hypersomnia nearly every day.
(5)	Psychomotor agitation or retardation nearly every day.
(6)	Fatigue or loss of energy nearly every day.
(7)	Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
(8)	Diminished ability to think or concentrate, or indecisiveness, nearly every day.
(9)	Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Despite the attention that has been paid to the development of MDD treatment, a favorable impact on MDD prevalence in the population has not been detected[18]. A potentially influential factor that might have contributed to MDD treatment being insufficient is the underestimation of sleep disturbances in the treatment of MDD. Previous studies have learned us a lot about the potential risks of sleep problems, the large burden of major depression, and how sleep problems and major depression can exacerbate each other over the years. However, although sleep has been acknowledged as an important factor with regard to the development and recurrence risk of MDD, interventions concerning sleep are often neither included nor mentioned in MDD treatment guidelines and protocols[19].

A possible explanation for the under-acknowledgement of sleep in MDD treatment

is that it is not well understood what the exact role of sleep is in MDD. Earlier studies on the role of sleep in MDD have been focusing on the effect of sleep at a time scale with long intervals, for example to investigate the influence of present sleep disturbances on the development of MDD one year later[20]. This type of studies is interesting and informative regarding the etiology of MDD. However, the long time-interval in this type of studies disables the possibility of investigating short-term changes that occur in MDD and exploring more precisely the temporal order at which these short-term changes occur. Studies with shorter time intervals and multiple repeated assessments are needed to investigate the temporal order of change among sleep and other relevant factors that are involved in MDD such as affect[21], physical activity[22], and melatonin[23]. Identifying the temporal order of change between sleep and these factors implicated in MDD matters, because knowing where change starts enables to indicate potential starting points in the treatment of MDD. This may help to identify the potential of targeting sleep parameters in the prevention and treatment of MDD.

There are some other methodological factors that have complicated MDD research. These factors are inherent to 'traditional' research approaches, by which I mean studies with a cross-sectional design, or panel design with a limited number of assessment waves, or studies that are performed in a laboratory setting. These studies do not connect well to what happens in clinical practice and the daily life of MDD patients for the following reasons: (1) dynamics are not captured, (2) heterogeneity among patients is not accounted for, and (3) ecological validity is low. I will discuss each of these problems in more detail below.

Dynamics

Change over time is one of the main characteristics of how affective disorders evolve[24]. Processes that are characterized by change, activity, or progress are called dynamic processes. It is known that MDD has a dynamic character[25]. MDD symptoms, affect, and underlying factors that are closely related to MDD, fluctuate from day to day[21]. Not knowing how short-term fluctuations in MDD-related variables (e.g., affect, cognitions, behavior, hormones) are related to each other and in what order they occur hampers progress in scientific research and MDD treatment because it leaves limited insight in day-to-day fluctuations and mechanisms involved in MDD. To uncover the temporal dynamics and the ebb and flow of variables involved in MDD, and to answer questions about the order in which fluctuations among MDD-related variables occur, it is necessary to perform studies with multiple repeated assessments that are frequently assessed at short time intervals[26]. Modeling short-term dynamics and the order of change over time has the potential to give a clearer insight in processes that evolve in MDD and provides potential starting points in the treatment of MDD.

Heterogeneity

The diagnostic guideline of MDD was based on descriptions of clinicians instead of empirical research, and has resulted in a very heterogeneous concept of the disorder[27,28]. An individual must suffer from at least five out of the nine available symptoms of MDD,

of which one must be a core symptom, to be diagnosed with MDD according to the guidelines of the DSM-V[4] (criteria see Box 1). This means there are up to 227 possible symptom combinations for a diagnosis of MDD[29]. Heterogeneity was even described as "the most salient feature of depression"[30]. The problem is that when such heterogeneous population of depressed patients is investigated at the level of the group, significant information about the variation among individuals is cancelled out. This has hampered adequate prediction of MDD outcomes in clinical practice[31], because an average representation of MDD patients cannot reflect the heterogeneity that is seen in clinical practice. Heterogeneity is not well accounted for in traditional studies because their focus is on average group results. This means that the average results that emerge from traditional research approaches do not mirror the actual behavioral patterns of MDD patients[32]. Studies with multiple repeated assessments are suitable to overcome this problem because such a design enables to take interindividual heterogeneity into account while group-level effects can still be estimated.

Ecological validity

A third difficulty in MDD research is the low ecological validity of some traditional studies. Ecological validity can be low because of several reasons: retrospective assessments, an unnatural setting, not taking environmental context into account, and the type of design that disables to model fluctuations over time at the person-level[33,34]. This restricted ecological validity decreases the translatability of study results to the daily life of participants. Although a traditional approach is informative to classify certain characteristics of a group, it is a disadvantage not to know how patients behave and feel in their own environment. Especially in light of the heterogeneous and dynamic character of MDD and the daily fluctuations of MDD symptoms and MDD-related variables, it is of great informative value to capture the flow of daily life in which MDD-related factors develop and change in the participant's natural environment.

Aim of this thesis

In this thesis the role of sleep is investigated in the context of everyday MDD from a physiological and a behavioral perspective by means of intensive longitudinal designs and relatively novel statistical techniques. Intensive longitudinal designs refer to a research approach in which series of multiple repeated measurements are collected within each individual. Intensive longitudinal designs result in time series: repeated assessments per individual over time. Ideally these repeated assessments are measured within a time frame that fits the process of interest, i.e. a short, within-day time interval to capture fluctuations in hormones, and a longer, between-day time interval to capture fluctuations in sleep.

Using different time frames is of substantial added value because this enables to gain

relevant complementary knowledge about the dynamic role of sleep[32,34]. This enables to answer questions about the temporal order of change during a dynamic process from several perspectives. For example, time series with within-day measurements enable to assess dynamics of a biomarker such as melatonin because fluctuations of the biomarker are expected to occur at a short time scale. Time series with daily measurements enable to assess dynamics of sleep. Lastly, time series with week-to-week measurements enable to examine fluctuations in symptoms of depression because symptoms are less likely to fluctuate much within the day.

An extra advantage of time-series data is the possibility to characterize person-specific processes, as the data can be analyzed at the level of the individual. Besides, the design with repeated assessments allows testing average patterns at the level of the group, while still taking differences among individuals into account. Therefore, this approach is very suitable to identify communalities as well as differences among patients, which may help to overcome the problem of heterogeneity among MDD patients[26,32].

Third, in intensive longitudinal designs most often ambulatory assessments are used to frequently assess participants within the context of their daily life. Ambulatory assessments cover a wide range of assessment methods to study people in their natural environment: for example self-report of depressive symptoms, affect, or sleep, objective monitoring of physical activity, and collection of biomarker data[34]. These assessments that occur in a natural and spontaneous context increase the ecological validity and thus translatability of study findings to daily life and clinical practice. To conclude, by using intensive longitudinal designs we can address dynamics, heterogeneity, and ecological validity while investigating the role of sleep from a physiological and a behavioral perspective.

In ***Chapter 2*** and ***Chapter 3***, the role of sleep is viewed from a physiological perspective. In ***Chapter 2*** I describe how endogenous melatonin secretion develops over time. Therefore stability, within- and between-day dynamics, and interindividual differences of endogenous melatonin secretion in MDD patients and healthy controls were investigated. ***Chapter 3*** describes how these within-day dynamics of melatonin secretion are connected to within-day dynamics of positive affect, negative affect, and fatigue, and vice versa. Besides, in this chapter, the association between interindividual differences in the role of melatonin secretion and depression severity and sleep-related factors was explored.

In ***Chapter 4***, ***5*** and ***6*** I explore the role of sleep from a behavioral perspective. ***Chapter 4*** describes the within-day temporal order of changes in sleep and affect in MDD patients and healthy controls, and whether these changes are mediated by fatigue or rumination. ***Chapter 5*** describes the within-day temporal order of changes in sleep and physical activity in MDD patients and healthy controls, and whether these dynamic associations are the same for MDD patients and healthy controls. In ***Chapter 6***, the bidirectional dynamic week-to-week association between sleep symptoms and core depressive symptoms in MDD patients is described and attention is paid to data-driven subgroups that differ based on the 3-year course of these symptoms.

Chapter 7, the General Summary and Discussion, is dedicated to the discussion of the main findings from abovementioned chapters.

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