A sad day's night

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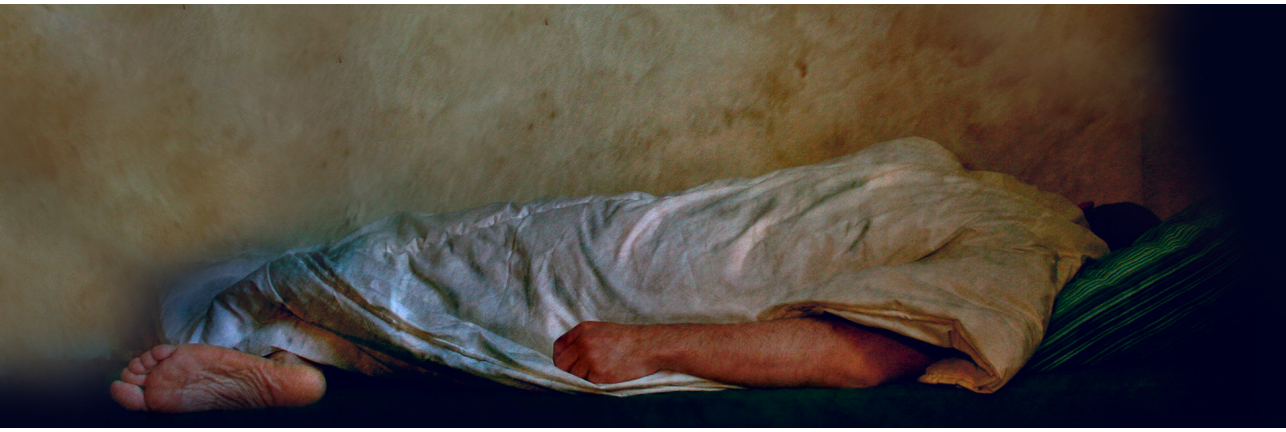
Chapter 7

General Summary and Discussion



This thesis was aimed at examining the role of sleep in the context of MDD from a physiological and a behavioral perspective. For this purpose intensive longitudinal designs with short time scales were used and relatively novel statistical techniques were applied. This approach enabled to examine short-term temporal dynamics between sleep and other MDD-related variables, and enabled to find out what possibilities there are to target sleep parameters in the prevention and treatment of MDD. In this chapter I will discuss the main findings, methodological considerations, clinical implications, and future research directions.

Dynamics

Earlier studies showed that sleep plays an important role in the development and recurrence of MDD[1-4]. The role of sleep at a shorter time scale has not been explored much[5], just as the temporal ordering among sleep and other variables like affect and physical activity, variables that are important in the context of MDD. I started with a physiological point of view and a within-day approach to explore within-day dynamics of the melatonin in ***Chapter 2*** and ***Chapter 3***. Then I moved on to a behavioral approach, and a day-to-day time frame, to explore the temporal dynamics between sleep quality and positive or negative affect in ***Chapter 4***, and to explore the temporal order of change between sleep quality or quantity and physical activity in ***Chapter 5***. In ***Chapter 6*** I used a design with a week-to-week time frame to investigate the bidirectional dynamic relationship between sleep symptoms and core depressive symptoms of MDD. In this chapter was also investigated how sleep and core depressive symptoms developed over a 3-year course, and whether subgroups could be identified based on differences in this course. Furthermore was investigated whether the identified subgroups could be characterized by differences in the bidirectional relationship between sleep and core depressive symptoms.

A physiological perspective on the role of sleep

Earlier studies pointed towards the potential importance of melatonin in the context of MDD[6,7]. Disrupted endogenous melatonin secretion levels were thought to be associated with episodes of MDD[6,7], and exogenous melatonin administration had been found to improve MDD status[8]. However, most studies applied a cross-sectional design or measured melatonin secretion for a maximum of 24 hours[9] and did not take possible intra- and interindividual variation in endogenous melatonin secretion levels into account. I therefore started by exploring the stability, within-day and between-day dynamics of endogenous melatonin secretion in depressed and non-depressed participants in ***Chapter 2***. Both depressed and non-depressed participants showed day-to-day variability in their endogenous melatonin secretion. On average depressed participants showed significantly more variance and higher melatonin levels than the non-depressed participants (p<.05). In ***Chapter 2*** was shown that in some participants, higher melatonin levels were association with time of antidepressant intake (evening intake). Next to these communalities at the level of the group, a high degree of interindividual variation in melatonin secretion was found. The dynamic nature of endogenous melatonin secretion

enabled to investigate whether these dynamics were related to dynamics in fatigue and positive and negative affect. In ***Chapter 3*** again depressed and non-depressed participants were investigated. In the majority of participants within-day changes in endogenous melatonin secretion were temporally or contemporaneously associated with within-day changes in positive or negative affect or fatigue, but with substantial interindividual differences in the strength and direction of the association. One explanation of these differences is heterogeneity between participants. An alternative explanation for these differences is that the findings at the level of the individual might represent a type I error (false positive). There were twelve possible associations between melatonin and affect or fatigue per participant. At an α-level of .05, this means that in at least 50% of the participants, the significant melatonin association could reflect a chance finding. Still, 83% of the participants did show associations of melatonin secretion with fatigue, positive affect, or negative affect, which suggests that the finding represents more than just a type I error. Participants in this group, with associations between melatonin and fatigue or affect, reported higher sleep quality than participants in who no associations were estimated between melatonin and fatigue or affect.

Overall, the findings of ***Chapter 2*** and ***Chapter 3*** do not point towards a specific role of melatonin dynamics in the context of depression. The results did not show characteristic associations of melatonin dynamics for depressed versus non-depressed participants. Remarkably, in a small subgroup of participants with most severe depression scores (N=4), melatonin dynamics were not associated with fatigue or positive or negative affect. A possible - but tentative - explanation for this finding is that there is often a lack of daily structure in patients who suffer from severe depression, which might be associated with the circadian rhythm being "out of tune". As a result, the natural ebb and flow of melatonin secretion levels (low in the morning, high in the evening), of affect (high in the morning, low in the evening), and of fatigue (low in the morning, high in the evening) could be dysregulated and therefore lose associations with each other. It would be interesting to further investigate if this idea is correct, to find out whether and how melatonin dynamics are associated with fatigue and affect in other severely depressed patients, and if so, to investigate whether applying a strict daily structure might be beneficial for these patients.

A behavioral perspective on the role of sleep

In ***Chapter 4***, ***Chapter 5***, and ***Chapter 6*** I changed to a behavioral perspective on the role of sleep in depression. I found that changes in sleep were unidirectional associated with day-to-day changes in affect and physical activity. In ***Chapter 4*** was shown that changes in sleep quality were associated with changes in subsequent positive and negative affect, but not vice versa. The temporal association from sleep quality to positive and negative affect was partly mediated by fatigue. Then, in ***Chapter 5*** was investigated whether day-to-day changes in physical activity and sleep quality or quantity were associated with each other. Again, changes in sleep were associated with subsequent changes in physical activity, but not vice versa. To be more specific: an increase in sleep duration was associated with a decrease in next-day physical activity. ***Chapter 6*** was aimed at investigating the dynamic association between sleep and mood during episodes of depression and remission. The results of this chapter showed that sleep not only plays a role in the development and

recurrence of MDD, but also affects week-to-week changes in core symptoms of MDD during depressive episodes, remission, and recurrence. This was also found the other way around: week-to-week changes in core symptoms were associated with the course of sleep symptoms of MDD during depressive episodes, remission, and recurrence. To be more specific: the current state of core symptoms was associated in next-week changes in sleep symptoms (either development or remission), and vice versa, the current state of sleep symptoms was associated with next-week changes in core symptoms. Contrary with the findings from ***Chapter 4***, in which a unidirectional association was found from day-to-day changes in sleep quality to subsequent affect, in ***Chapter 6*** a bidirectional association was found between week-to-week changes in sleep symptoms and core depressive symptoms. A second aim of ***Chapter 6*** was to derive meaningful subgroups that differed in their 3-year course of sleep symptoms and core depressive symptoms. I identified 3 classes that were substantially different during the 3-year course of sleep symptoms and core depressive symptoms. The 1st class was characterized by persistence of both symptoms during those 3 years, and a unidirectional association from week-to-week changes in sleep symptoms to subsequent core depressive symptoms. In the 2nd class both symptoms remitted and a bidirectional association between sleep symptoms and core depressive symptoms was found. In the 3rd class the sleep symptoms remitted less steeply than the core symptoms during those 3 years, while no association whatsoever was found between week-to-week changes in sleep and core depressive symptoms.

In conclusion, the abovementioned chapters suggest that sleep dynamics play a role in behavioral aspects of depression. Most interesting is the contradiction in results between day-to-day and week-to-week intervals. Investigating day-to-day dynamics resulted in a unidirectional association in which sleep dynamics always preceded dynamics in affect or physical activity. Contrary, when week-to-week dynamics were investigated, a bidirectional association was found between sleep and core depressive symptoms. Possibly, sleep responses slower to change than affect and physical activity, and therefore associations between affect or physical activity and subsequent sleep can only be detected in studies with a time interval of a few days. Another explanation could be that sleep is less responsive to change than affect and physical activity. Lower responsiveness would explain why changes in sleep were only detectable in the design where sleep and core depressive symptoms were assessed weekly instead of daily.

Heterogeneity

The application of intensive longitudinal designs enabled to overcome the problem of heterogeneity that was mentioned in ***Chapter 1***. Interindividual differences were taken into account in every chapter of this thesis, and in each chapter substantial intra- and interindividual differences were revealed. Both depressed and non-depressed participants showed intra- and interindividual differences in the examined associations. Taking these differences into account added relevant information that would otherwise have remained undetected, especially in ***Chapter 2*** and ***Chapter 3***, namely that melatonin secretion levels are not that robust (***Chapter 2***) and that associations at the level of the group do not always

resemble associations at the level of the individual participant (***Chapter 3***). Significant information would have been overlooked or lost would we not have examined individual patterns in both chapters. Both results show that the investigation of heterogeneity can add relevant information about fluctuations within participants and differences therein between participants who are part of the same group. In ***Chapter 4*** and in ***Chapter 5*** we also found substantial interindividual heterogeneity in the strength and direction of the examined associations. Significant associations were found at the level of the group despite this heterogeneity among participants. The same holds for the results of ***Chapter 5***: significant group-level associations were estimated despite substantial interindividual heterogeneity in the strength and direction of the temporal association between sleep duration and subsequent physical activity. Differences in strength and direction of the temporal associations could not be attributed to diagnostic status in any of the abovementioned chapters. In the study of ***Chapter 6***, in which only MDD patients were included, interindividual heterogeneity was taken into account as well. Despite the heterogeneous character of MDD, significant associations that predicted the likelihood of changes occurring at the level of the group and at the level of three subgroups could still be estimated.

In conclusion, this thesis shows that heterogeneity should be taken into account because this results in additional knowledge that would otherwise remain unnoticed. Besides, the amount of heterogeneity shows the need for tailor-made interventions, because the interindividual differences emphasizes that average associations at the level of the group are not always representative for the strength and direction of the association at the level of the individual.

Ecological validity

The third factor that I considered as a difficulty of more traditional approaches was the restricted ecological validity. The ecological validity of the MOOVD data was relatively high: ambulatory assessments were used to monitor affect and behavior thrice a day with 6h-intervals. The participants collected the data in their natural environment, fluctuations over time were modeled, and interindividual heterogeneity was taken into account[10,11]. This increased the translatability of our study results to daily life of depressed and non-depressed people. The data that were used in Chapter 6 were less precise because of longer time intervals between measurements and the retrospective design. Weekly symptom presence was assessed once every 3 months, not every week. Still, the ecological validity of this study was higher than more traditional studies because participants' symptom course was monitored in their natural environment, and because the longitudinal design enabled to investigate fluctuations over time at the person-level[10,11].

Methodological considerations

Intensive longitudinal data

The use of intensive longitudinal data enabled to investigate the role of sleep from a different point of view. It was possible to model temporal dynamics, heterogeneity was taken into account which revealed otherwise unnoticed information, and results had higher levels of ecological validity. However, there are some factors that should be kept in mind with regard to intensive longitudinal designs.

A major difficulty of intensive longitudinal designs is choosing the time interval and the duration length of the study. As already mentioned in ***Chapter 1***, the time interval depends on the type of research questions at hand. The difficulty is that most often there will be more than one question to be answered: the datasets that emerge from intensive longitudinal designs contain a lot of information on several parameters. For example, the MOOVD study contained over 60 parameters. The time between intervals and duration of the study should be chosen in such way that fluctuations in multiple types of parameters can be captured. In our case, it was unfortunate that we had "only" 30 measurements of sleep in the MOOVD dataset, because sleep fluctuates between and not within days. This disabled the inclusion of the sleep measurement in the GIMME analyses of ***Chapter 3***. On the other hand, the MOOVD dataset was quite unique: because melatonin fluctuates within days, we had up to 90 measurements of melatonin, and we therefore could unravel questions about stability and day-to-day stability and change that had remained unanswered up to now.

Another point that should be kept in mind is that even though intensive longitudinal designs open up interesting ways to look at a certain topic, it is a time-consuming and expensive way to perform research. I would therefore advise to only use this approach in case more traditional designs give unsatisfactory answers and a closer look at a dynamic process or information about individual differences is needed.

Modeling temporal dynamics

A major methodological advantage of intensive longitudinal data is the possibility to model temporal dynamics of change and thus the order of effects between parameters. This is not possible with cross-sectional or panel designs with only a few assessment waves. In fact, knowledge about the order of change is a major step forward towards knowledge about causality. However, a fundamental mistake that is often made is that when temporal associations are estimated, this would equal causality between parameters. Articles often discuss how parameter x "influences" parameter y, and how changes in parameter y "caused change" in parameter z. For sake of comfort we tend to use terms that imply causality but this is not the case. Nonetheless, when approaches like the ones in this thesis are used, results always consider associations instead of causation. In that regard the term "Granger causality"[12] is unfortunate and can be misleading, because strong evidence of Granger causality may be weak evidence of a causal relationship between variables. Of course the type of the design can make a researcher suspect a causal relationship between parameters, but the only way to truly investigate causality is by an experimental

intervention study in which the suspected cause will be triggered to find out whether this influences the suspected reaction. I will further elaborate on this in the paragraph *Future Directions*.

In this thesis I used several statistical approaches to investigate temporal dynamics from a time series perspective (***Chapter 2-5***) or from an epidemiological perspective (***Chapter 6***). In ***Chapter 2*** we used autoregressive integrated moving average[13] (ARIMA) modeling because we wanted to model individual time series. This is a useful approach in case the dynamics of individual time series have to be mapped. In case individual time series' interdynamics should be analyzed at the level of the group ánd the individual, group iterative multiple model estimation[14] (GIMME; ***Chapter 3***) is a more suitable approach. The benefit of this approach is that multiple individual time series can be analyzed simultaneously at the level of the group and at the level of the individual. Obviously this method also has some disadvantages. The first difficulty of GIMME is that the contemporaneous associations are pointed in a direction, which suggests a certain ordering in the association. Statistically the ordering can be explained by the fact that when multiple parameters are modeled, parameter x can explain a larger part of the variance in parameter y, than parameter y explains of the variation in parameter x, because other parameters also explain a certain amount of the variance in x and y. Explaining this theoretically becomes much more of a challenge, because the question how temporal ordering can be detected in parameters that were measured at exactly the same moment in time, is very difficult to answer. GIMME developers suggest that directed contemporaneous associations reflect relations occurring at increments less than the measurement interval. In my opinion modeling unmeasured fluctuations that occur within an interval is statistically impossible. I would therefore advise to explain this directed association only as a matter of differences in the percentage of explained variance.

In ***Chapter 4*** and ***Chapter 5*** a multilevel approach was applied. This approach is of great use when the researcher is interested in average group associations and wants to take individual heterogeneity in these associations into account. In multilevel modeling, a normal distribution of parameters is assumed. When data is largely heterogeneous and in case multiple subgroups with substantially different parameter distributions are present, modeling average results will be of little added value because the average group result will not mirror associations at the level of the individual. A major advantage of GIMME in comparison to multilevel modeling is that not average levels but the number of participants that show a certain association are considered. The number of participants that should show the same association can be randomly chosen by the researcher, which is another disadvantage of GIMME analyses. The criterion of >75% to represent the majority of the sample should be followed as a cutoff score[14]. An advantage of manipulating the criterion is that the researcher can raise the percentage to test the robustness of the findings, for example whether the findings hold in >95% of participants. In the multilevel modeling, best linear unbiased prediction[15] (BLUP) was used to estimate the strength and direction of the individual associations. The estimated BLUP coefficients do not provide information about the exact association at the level of the individual. Therefore, this approach is less suitable when the researcher is interested in effects that occur at the level of the individual.

Lastly, in ***Chapter 6*** Manifest Markov modeling[16] was used. This approach is especially suitable when a researcher is interested in moments of change. Drawback of this method is the assumption that only the measurement at t-1 influences these moments of change. Besides, although Manifest Markov modeling enables to investigate patterns at the level of the group while taking individual heterogeneity into account, the model does not provide information about interindividual heterogeneity or random effects.

It may be clear that the choice of method largely depends on the research. In conclusion, I would advise the following: if the individual-level associations are most important, use methods that analyze the data at the level of the individual such as ARIMA or VAR. If the main interest lies in average group-levels and the degree of heterogeneity I would advise a multilevel approach or Manifest Markov modeling, and if the main interest lies in communalities of individual-level associations, GIMME would be the appropriate method.

Clinical implications

This thesis stresses that dynamics of sleep are associated with MDD core symptoms and MDD-related factors fatigue, affect, and physical activity. The findings hold some suggestions for clinical practice, which I will further discuss below.

The first implication is related to melatonin secretion. One of the findings of ***Chapter 2*** was that the time of antidepressant intake might mediate the effect of the antidepressant on melatonin secretion, because increased melatonin secretion was associated with evening intake of citalopram and amitriptyline. Heightened melatonin secretion levels may induce daytime feelings of fatigue[8]. Increased fatigue is a disadvantageous side-effect, especially in the context of MDD, because depressed patients already report higher feelings of tiredness throughout the day. Therefore the clinician should pay attention to this potential side-effect of antidepressants on melatonin secretion and eventually change the time of intake to find out whether this benefits the patient.

The second implication is related to associations of sleep with affect, physical activity, and core depressive symptoms. ***Chapter 4***, ***5***, and ***6*** showed that changes in sleep were associated with subsequent behavioral changes, and in case of ***Chapter 6***, changes in core depressive symptoms were also associated with subsequent changes in sleep. Altogether these temporal associations suggest that sleep plays a role in behavioral aspects that are related to depression in both depressed and non-depressed people. A sleep-oriented approach might therefore be beneficial in prevention and treatment of behavioral aspects such as negative affect, low physical activity, and sad mood. Unfortunately, clear-cut advice about the effects of sleep on behavior and depression course cannot be given because causality was not investigated in this thesis (more on this in the paragraph *Future Directions*). On the other hand, I'm not aware of cases in which improvement of sleep ever harmed people. Knowing that the absence of sleep disturbances is associated with a lower risk of future health complaints compared to the presence of sleep disturbances[17,18], makes me question why sleep did not yet receive more attention in clinical practice. Therefore I would recommend starting implementing basic sleep hygiene advice in clinical

practice. Examples of sleep hygiene advice are: always go to bed at the same time, sleep in a dark, cool, silent room, avoid alcohol, caffeine, and heavy meals before sleeping, practice exercise during the day, don't nap after 4pm, and do relaxation before sleeping. This may be a first step towards carefully implementing a sleep-oriented approach in clinical practice. Stronger recommendations can be made after thoroughly investigating causality between sleep and behavior.

The finding that substantial interindividual differences were found in the strength and even direction of associations in each chapter of this thesis emphasizes the need for a tailor-made patient approach. Most treatment advice is based on average group results and therefore the advice does not mirror the patient in front of the clinician. The abovementioned advices should be taken into consideration in the light of this heterogeneity, and should be adapted to individual needs of the patient. Finding out what works for each individual patient by means of an intensive longitudinal approach (i.e., diary study) would be too time-consuming and intense in terms of patient burden and workload for the clinician. I therefore recommend keeping in mind that sometimes the average treatment approach will not work for the patient, and in that case, the patient might benefit from keeping a daily diary so that dysfunctional patterns over time can be mapped.

Future directions

The most important recommendation for future research concerns the investigation of causality. It would be of great informative value to find out whether experimentally manipulated changes in sleep quality or quantity can actually predict beneficial changes in behavior associated with MDD, in MDD core symptoms, or in MDD course. Knowing this would finally provide clear-cut starting points for prevention and treatment. If the treatment of sleep disturbances point out to be beneficial, targeted treatments can be implemented in clinical practice, which may eventually lead to a decrease of MDD prevalence. Not only knowing that sleep is associated with MDD, but also knowing how we can start taking advantage of this might benefit the prevention and treatment of MDD.

Another important factor to keep in mind in future research is that although sleep is now a popular topic and seems important in the prevention and treatment of MDD, there are several other factors that should be investigated as well. The contribution of sleep is not unique. As long as dynamics, heterogeneity, and ecological validity are considered, future research will bring us closer to a tailored approach of MDD in which we know what treatment works best for whom.

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