Chapter 11
General discussion
In this thesis we studied the relationship between chronobiology and mood disorders. The first part describes vulnerability factors for mood disorders, such as genetic factors and chronotype, the second part looks into the direct relation between sleep-wake rhythms and mood using actigraphy and the third part studies therapeutic options influencing chronobiological mechanisms. Different types of studies varying from large cohort studies to small scale, in-depth clinical pilot studies are used to investigate chronobiological mechanisms in mood disorders. In this general discussion, the most important findings will be summarized and possible pitfalls of the work, suggestions for future work and clinical implications will be discussed.

**Part 1: Vulnerability factors for developing mood disorders**

Underlying genetic predisposition for mood disorders within circadian genes.

In chapter 2 we looked at a large sample of patients with major depressive disorder in the Netherlands. We studied the relationship between genetic markers in pre-selected genes, chronotype and mood disorders, to see if there is an underlying genetic predisposition for mood disorders, mediated by chronotype. We found that 13 genetic markers within six genes were significantly associated with chronotype, and 59 genetic markers within 18 genes were significantly associated with mood disorders. Of these genes one showed a possible mediating effect of mood on chronotype, which did not survive correction for multiple testing. Looking at specific gene clusters, although none were found to represent any neuronal process, one cluster was found to be associated with metabolic syndrome, which has been associated with MDD before (1). Finding this cluster within circadian genes linking mood disorders to metabolic syndrome is of special interest, as also circadian regulation and metabolic syndrome have been studied before (2). It is important to realize that we did not conduct the analysis with metabolic syndrome in mind, so it is a chance finding which has to be replicated before drawing strong conclusions.

Chronotype is frequently suggested as a vulnerability factor for developing, or causing a worse course, of major depressive disorder (3–5). This is the case for the evening chronotype where people have a preference for a later timing of activities (5). This is because people with an evening chronotype experience more social jetlag, where the preference of timing is misaligned with the socially accepted timing (6–8). An example of this are adolescents who typically have an evening chronotype, while school timing is all directed towards early morning activities (9–11).

Is social jetlag related to major depressive disorder?

In chapter 3 we studied whether social jetlag is actually associated with the MDD diagnosis and how it relates to depressive symptoms in patients and healthy people as well. In our study patients with MDD did not show more social jetlag compared to controls,
furthermore there was no relation between social jetlag and depression severity. This lack of a group difference shows that although patients are more likely to be evening types, the relation between chronotype and MDD cannot be explained by social jetlag. Another reason why patients in a current depressive episode show a later chronotype is reactive to the depression, instead of a cause of the depression. Patients with MDD often show a diurnal preference, with less depressive symptoms in the evening compared to the morning (12,13). A reaction to this preference might be a shift of activities towards the evening in these patients, when patients experience less mood symptoms. As we evaluated chronotype with a questionnaire concerning their daily rhythm (sleep times on work and free days), this change in behavior might be reflected in the chronotype.

Problems with studying chronotype in patients with different states of the disease
In chapter 4 we discussed the difficulties with the interpretation of evening chronotype and depressive episodes. The key question in this chapter was whether the evening type is a state effect of a depressive episode, or if it is a vulnerability factor. Although the recent literature suggests it is a vulnerability factor, we hypothesize it might be a state effect.

Part 2: Rest-activity rhythms and mood – actigraphy
The second part of this thesis (chapter 5-8) focused on bipolar disorder and actigraphy measures. Especially the link between rest-activity rhythm disturbances and mood with the different stages of the disease were studied.

Do patients with bipolar disorder show circadian rhythm disturbances in the euthymic phase of the disease compared to controls?
In chapter 5 we examined rest-activity measures in euthymic patients with bipolar disorder, by conducting the largest actigraphy study to date in patients with bipolar disorder type I, while studying unaffected siblings and healthy controls as well. In this sample, we looked whether patients with BD in a euthymic phase still experienced circadian rhythm disturbances, by looking at their rest-activity rhythm as measured with actigraphy. Patients did not show less stability between days, variability within days nor a less robust amplitude compared to controls. This is an interesting finding, especially as we know that patients in a current mood episode do show rest-activity rhythm instability (14). Our results show patients are capable of maintaining a healthy circadian rhythm in their euthymic phase. There might be a selection bias in this sample, as all patients were medicated and were already familiar with the disorder for quite some time. As both pharmacological and cognitive behavioral therapy in bipolar disorder aim to stabilize rest-activity rhythms as well as mood, this might be a
possible confounder. Previously we showed similar results for sleep variables: euthy-
mic patients showed no differences in sleep variables compared to controls (15).

Can rest-activity patterns function as an early warning signal of imminent mood changes in a single subject?
Chapter 6 shows an example of how actigraphy may be used for direct clinical benefit in one individual patient, and how rest-activity patterns might be an early warning signal for imminent mood changes. A patient with bipolar disorder experienced a major life event while participating in a two-week actigraphy protocol. We described how her actogram, the graph of her activity, reflected the life event. In the night following the life event she experienced a later sleep onset and a shorter sleep duration. As the patient noticed the change in mood as well, she reacted adequately by taking loraze-
pam for two nights, prescribed by her psychiatrist, which resulted in two good nights of sleep and no further mood disturbances. This adequate reaction to a disturbed night of sleep might have prevented a relapse into a full mood episode. In this chapter, we discussed how ambulatory assessment with actigraphy, together with the patients' own experience could be useful in predicting relapses.

The temporal relation between sleep and circadian disturbances and mood in the onset of a mood episode.
Based on this experience we conducted a new study, studying 13 patients with bipolar disorder for 180 days with both actigraphy and a sleep and mood diary to test the temporal order between mood and sleep symptoms. In chapter 7 we explored this relation with a novel method, studying both mean shifts in sleep variables (i.e. slowly sleeping less and less) and sudden peaks (such as one night of disrupted sleep) in the onset of a manic or depressive episode. To our knowledge, this is the first study of such scale, and with such frequent measurements looking specifically at this transition in the patients' own daily life. We found that in two of the eight subjects with a mood transition the mood episode was preceded by sleep disturbances. When using a less restrictive method, we found that specifically in the onset of a manic episode the mood changes were preceded by sleep disturbances, while in the onset of a depressive episode the sleep disturbances came after the onset of mood symptoms.

Can fractal patterns function as a marker for bipolar disorder?
In chapter 8 we again used the data from chapter 5 and 7 to look at another measure which can be derived from actigraphy, the fractal pattern. Fractal patterns are patterns which show a similar structure on different scales (16–18). These fractals patterns are also found in human physiology and this fractal pattern is often interpreted as a marker of good homeostatic regulation. The loss of this pattern has been associated with diseases such as Alzheimer’s disease and major depressive disorder (18,19). In chapter 8 we studied the cross-sectional data from chapter 5 and the longitudinal data from chapter 7. All activity data from wakefulness were analyzed for fractal patterns using a Detrended Fluctuation Analysis (DFA). From the DFA a scaling exponent is derived on different time scales. An ideal scaling component has a value of about 1. A value lower
than 1 indicates a random pattern, while a value above 1 indicates a smooth pattern. The scaling component on small time scales ($\alpha_1$, from 5 minutes up to 90 minutes) has been shown to be higher in depressed patients before [20]. The scaling component on larger time scales ($\alpha_2$, from 2 to 10 hours) has been shown to go to a random pattern when the suprachiasmatic nucleus (SCN) is lesioned [21,22]. In chapter 8 we showed that patients with bipolar disorder have a higher $\alpha_1$ compared to their siblings and healthy controls. Further analysis showed this was only the case in female subjects. Female patients, and female unaffected siblings, also showed a lower $\alpha_2$ compared to controls, indicating a possible genetic relation between $\alpha_2$ and vulnerability towards bipolar disorder. On the other hand, male patients showed a higher $\alpha_2$ compared to controls, which was unexpected and could not be explained by post-hoc analyses. In the longitudinal sample, no differences in the scaling components on both timescales were found between mood states. A relationship between more depressive symptoms and a lower $\alpha_1$ on a later time point was found in both the weekly and in the daily scores. The higher $\alpha_1$ in female patients, together with the lack of differences between mood episodes, show an interesting possible biomarker for bipolar disorder, especially because the scaling component is derived from a relatively cheap and non-invasive method. Replication is needed, but fractal patterns might be a promising route for biomarkers in bipolar disorder, and possible in more mood disorders.

**Part 3: Therapeutic options with chronobiological mechanisms**

The last part of this thesis is focused on chronobiological treatment options for mood disorders.

**Duration and timing of light therapy for seasonal affective disorder**

In chapter 9 and 10 we retrospectively studied a large sample of patients with seasonal affective disorder, by combining data from earlier studies that investigated different types of light treatment. All data from individual studies were pooled and analyzed. In chapter 9 we focused on the duration of light therapy, as we compared the effect of light therapy given for one week with light therapy during two weeks. There were no differences in therapy outcome between one and two weeks, only the speed of the recovery from depressive symptoms was faster in the group that received one week of therapy. As patients were already familiar with the length of the treatment, we hypothesize that the expectation of another week of light therapy might delay the effect of the treatment in the two-week group. To further understand the effects of expectations, we looked at the relation between expectations of the treatment and actual therapy outcome, and only in women we found a positive relationship between the expectations and outcome. This link between expectation and therapy outcome is an interesting construct to study, especially because this expectation has been suggested to be a mediator in pharmacological treatment of patients with major depressive disorder as well [23,24].
In chapter 10 we focused on the timing of light therapy. It has been suggested that for an optimal effect of light therapy patients should be given light therapy at a time based on their own chronotype (25). Patients with an earlier chronotype should be administered light therapy as early as 4:00 am, while later chronotypes should be given light therapy as late as 8:45 am. In our sample from the University Center Psychiatry in Groningen, all patients were administered light at 8 am, independent of their chronotype. This time would be most ideal for later chronotypes according to the protocol from the literature (25). As chronotype was assessed before the start of therapy, we could check whether the evening chronotypes have indeed more therapy success compared to morning types. This was not the case, we found a good therapy outcome in all study participants, independent of chronotype. This indicates that light therapy in the early morning might be sufficient for treating SAD and that the timing the light therapy optimally to the patients chronotype is not necessary.

**General discussion**

State or trait? A key question.
Rhythm and blues are heavily intertwined and changes in one domain may result in changes in the other (26,27). However, in this thesis we have shown that the associations between rest-activity disturbances and mood disorders are often not as straightforward as we had expected when these studies were initiated. For example, in the relationship between social jetlag and depression it seems that patients with MDD do not necessarily show more social jetlag than healthy controls, as found in chapter 3. In other study which do show a relation between the evening type and major depressive disorder, this result is typically found in patients who are in a current depressive episode (28). This suggests the evening chronotype is more a state feature (depending on a mood episode) than a trait feature (independent of mood episodes). Similarly, in chapter 5 we did not find disturbances in circadian variables derived from actigraphy in the largest study in euthymic patients with bipolar disorder to date. This also suggests that circadian disruption is not a trait feature of the disease, but could still be a state feature.

On the other hand, in chapter 2 we found genetic markers within a set of circadian genes for both chronotype and mood disorders, and no mediating effect of chronotype on the prevalence of mood disorders. As the subjects we tested in chapter 3 and 5 were in remission, a possibility would be that patients simply do not show circadian disruptions anymore as they have less mood symptoms, as they are all under a treatment (29). To gain further understanding of the temporal interplay between rhythm and blues we set out to study the relation between sleep-wake disruptions and mood symptoms in a patient sample in chapter 7, finding that in almost all subjects the sleep disturbances co-occur with a change in mood, which makes the relationship between mood symptoms and sleep symptoms even more clear.

Although we did not find a clear trait feature in the circadian measurements from actigraphy, if we look at fractal patterns in the activity in patients, unaffected siblings and controls, we did find a significant difference in the scaling component on small time-
scales. As we did not find any differences within subjects between a stable period and both manic and depressive periods, a state effect of this scaling component is unlikely. Not only the scaling component on smaller time scales, but also the scaling component on larger time scales, which is hypothesized to be regulated by the circadian timing system, is disrupted in female patients and their unaffected siblings. This effect is similar to what is seen in rats with a lesion in their suprachiasmatic nucleus, making the hypothesis of a link between the circadian timing system and this scaling component more likely (21). These results indicate the regulation of this complex system might be compromised, independent of state, specifically in female patients.

Methodological considerations
Circadian rhythm or rest-activity rhythm?
An important consideration, and for some a limitation, is how we assessed circadian rhythm in this thesis. One might even ask if this thesis studied the circadian rhythm at all (30). By using a questionnaire to assess chronotype and by using actigraphy as a measure of circadian stability, the actual circadian rhythm is not assessed under optimal test conditions; we have only looked at rest-activity rhythms in real life. Ideally a subject is studied in controlled conditions, for instance in a forced desynchrony protocol, where a subject is asked to sleep on an either very short or very long cycle for a longer period (20- or 28-hour day). As the circadian system cannot entrain to these extremes, it remains at its own endogenous period, and runs independently of the sleep-wake cycle. This allows the researcher to study the circadian component of a variable and the sleep component, independent of each other. However, forcing a patient with bipolar disorder out of their daily, Zeitgeber-synchronized, rhythm is highly unethical, because this may trigger a full-blown mood episode, which can take a long period to recover from. Another method to study the circadian rhythm is to measure the internal phase of that rhythm by studying the output of the circadian clock, the pineal hormone melatonin (31,32). Melatonin can be collected from saliva under dim light conditions to prevent light influences on the melatonin levels. By assessing saliva melatonin in the evening, the Dim Light Melatonin Onset (DLMO) can be derived. The DLMO is an interesting and relatively easy phase marker to assess. However, melatonin profiles are costly to analyze and the requirement of dim-light makes studying day-to-day behavior unpractical for regular clinical care. The methods used in this thesis, the chronotype questionnaires and actigraphy have been linked to internal phase in a number of studies. Both chronotype questionnaires, the morningness-eveningness questionnaire and the Munich Chronotype Questionnaire have been validated to each other and to the DLMO, showing good correlations (11,33–35). This shows that although we did not use the best method to assess phase, we did use the most suitable method for our purposes.

As we aimed to study patient in their own daily life, actigraphy is the most suitable method (36,37). It is non-invasive, and also minimally disruptive to the patients’ behavior. Actigraphy is well-validated for assessing sleep parameters and circadian parameters, also specifically in patients with bipolar disorder (37). As outcome measures we used the non-parametric variables, which are capable of capturing more than just the circadian rhythm (38,39). Interdaily stability (IS) measures the synchronization of the
rhythm to external Zeitgebers, Intradaily variability (IV) is a measure of fragmentation and the relative amplitude (RA) is the ratio of the activity during the most active 10 hours (M10) and the activity during the least active 5 hours (L5). This ratio is considered the amplitude of the rhythm, which can be seen as the power of the rhythm. The start-times of L5 and M10 are a variable related to the timing of the rhythm. A limitation of using this measurement is the number of days needed for a reliable estimate of these variables, which is at least a week to 10 days (40). In this thesis, we used at least 14 days for the estimates. An opportunity would be to explore the different methods to calculate these variables. For the analyses in this thesis the average activity of an hour is used for the calculation of the variables. A recent paper showed other bin sizes, shorter than the hour used here, may give a more precise method to detect both fragmentation (IV) and synchronization (IS) (41).

Another limitation relevant to the work in this thesis is the lack of light measurements. Although light measurements are possible with actigraphy, they are mostly unreliable and take up a lot of storage on the device. Furthermore, it would require continuous attention from the participants to not put their sleeve over the light sensor, which made it unsuitable for the studies conducted for this thesis.

Objective or subjective sleep measures
The work in this thesis is focused exclusively on objective measures of the rest-activity rhythm, either measured with a questionnaire studying the timing of sleep, or with actigraphy using sleep diaries only as a method to validate the sleep periods. No subjective measures of sleep duration and, possibly more importantly, sleep quality have been used to study patients. In the sample of patients with bipolar disorder subjective measures are assessed as well and can be studied at a later stage. However, we chose not to study the subjective measures, as we were trying to find the temporal relation between mood and objective sleep measures, without a masking effect of the interpretation of the patient. This is important, as for instance in an upcoming mania, patients might report a good sleep quality and no fatigue, while differences are definitely found in the objective sleep measures. In contrast, it has been shown that in remitted patients with bipolar disorder objective and subjective sleep and circadian measures correlate very well (42). Whether this is the case for these measures in, or in the transition to, a mood episode as well remains unclear.

Studying a temporal relation
Recently, alongside the possibilities of studying patients for a longer period, the possible methodologies to study their behavior has increased as well (43,44). In chapter 7 we used a novel method for the temporal relation which has not been used before. We specifically wanted to see how sleep and mood symptoms were related in the transition to a manic or depressed episode in patients with bipolar disorder. In our method outliers are used to visualize the influence of, for instance, one short night. This method using outliers is more commonly done in statistical processing (45). We expanded
the analysis with a changepoint analysis to be able to study the slower changes, for instance a decreasing sleep duration day by day as well (46). A simpler method, such as a cross-correlation function analyzing one sleep variable to one mood variable might have been easier, but a lot of information would be lost with this method (47). Re-analyzing the sample with different methods, which are yet under development or to be developed, is possible and would be interesting to do.

Medication use in patients with mood disorders
An important limitation of the work in this thesis is medication use in patients with mood disorder. In the chapter about social jetlag we accounted for antidepressant medication, and this showed that the small differences within social jetlag between patients and controls was partially explained by the fact that patients used medication. In the chapters studying patients with bipolar disorder, taking medication use into account is difficult because patients tend to use different types of medication that may have different mechanisms of action (48). Important to note is that lithium, the first-choice treatment of bipolar disorder, has an effect on the circadian rhythm and is one of the possible working mechanisms (49,50).

Secondary analyses of treatment studies
In the last part of the thesis, all patients with seasonal affective disorder (SAD) who have been studied, were treated with light therapy. Data from different treatment studies were combined into one dataset. This means that, although we had a large sample of SAD patients who were assessed with similar instruments and procedures, we performed a secondary analysis using data that had not been collected with the specific aim to study optimal light therapy duration and timing. On top of that, a randomized trial would be best suited to answer the optimal duration and the timing question. For the timing question patients could be randomized into two treatment arms, one with exact timing to the chronotype of the subject and one with light treatment at 8 am. However, the overall good treatment effect, with a response rate of 78%, found in chapter 10 and the lack of differences between chronotypes indicates that finding differences between these groups would require a large sample size. This would also suggest that the clinical relevance of making such a distinction would be limited.

Future directions and future research
Ambulatory assessment in real time
Although ambulatory assessment and studying actigraphy measures in mood disorders has been around for decades, recent technological advancements have resulted in a number of opportunities for this field (51). For one, all work in this thesis analyzed the data retrospectively, after an event occurred. In other words, we received the actiwatch data after a patient had experienced sleep disturbances and mood symptoms. There is currently still no real-time method to read out the data. However, advancement of commercial products similar to actigraphy suggests that using real-time data for analyses is only a matter of time. Especially in patients with bipolar disorder, 86% of the patients show an interest in using consumer products to aid their self-management strategies (52). A number of requirements however need to be met to make this possible (51). First
of all, the device should have a large enough storage to store multiple days. Secondly, a high enough resolution, ideally of at least activity counts every minute (epoch length of a minute), is necessary for reliable calculations. The third requirement is that the device is not only capable of storing this data multiple days, but also able to function for for multiple days without need for recharge. Current devices often have to charge overnight, which would make sleep analysis impossible as the device is not worn overnight. The fourth requirement is that the activity data is freely, and in raw format, available to not only the patient, but also the clinician and researchers. A continuous stream of raw data would allow real time algorithms to search for patterns in these data and study the rest-activity rhythm of the patient at each time point. Currently this is not the case. In chapter 7 there was one participant wearing a commercial activity device alongside the actiwatch, which illustrated another aspect, namely that due to lack of openness from the manufacturer data could not be derived from the device to be studied next to the actiwatch data. The fifth requirement is the validation of these devices. Are they actually able to measure sleep as they promise, which is currently not the case for most devices (53).

Using commercially available devices might be an interesting way to study more patients for a longer time, each with their own device and possibly also with their own personalized diaries. However, important to note is that not only good things come from self-registration of the patient. A recent case-series presented patients with orthosomnia, where the main sleeping problem was the preoccupancy with the feedback from the device, instead of their subjective sleep quality (54). This preoccupancy resulted in more anxiety about their sleeping problems, resulting in symptoms of insomnia, which in these patients were specifically hard to treat.

**Integrating ambulatory assessment in clinical practice**

Although actigraphy is a good example of how ambulatory assessment could assist the clinician treating patients with mood disorders, as we showed in chapter 6, moving from ambulatory assessment for research to clinical implementation is not as easy as it may seem. Significant steps have been taken to capture more personalized and precise patterns of symptoms of individual patients over time (44,45), and ambulatory assessment of individual symptom networks have been used to develop tailor made and focused treatments for specific patients (43,44,55). Such personalized diagnosis and treatment could have benefits for clinical practice, but larger trials are needed to show that this may indeed be of help in the diagnostic, and therapeutic process.

**Automation of sleep and circadian measures**

In multiple chapters of this thesis sleep and circadian measures are calculated using different types of programs to derive these measures. Future work should focus on making these type of analyses more accessible to the general public. Most of all as the required skills for these analyses are not typically the skills a clinician or interested researcher might have. For this thesis we developed our own script (ACTman, available from [https://github.com/compsy/ACTman/](https://github.com/compsy/ACTman/)), which is publicly available to everybody who might be interested in analyzing sleep and circadian rhythmicity. It can be used in the open-source statistical program R (56,57).
State or trait
Although we did study the state/trait feature quite elaboratively for bipolar disorder, the question remains whether chronotype is a stable trait feature, or more dependent on the mood state. Ideally the same participant would be assessed a number of times over the years, to see how chronotype might change across age, occupation and most interesting, how it might change depending on the state of the disease. The Netherlands Study of Depression and Anxiety, which was used in chapter 3, might be suitable for such an analysis, as the same patients are followed year after year. Using such an elaborative database might give the final answer on the stability of chronotype over different states of major depressive disorder.

Sleep deprivation as an antidepressant
Although this thesis aimed to further our understanding of the chronobiological underpinnings of mood disorders, a lot remains to be studied. For example, an important application of chronobiology in mood disorders has not been mentioned at all in this thesis, namely treatment of depression with sleep deprivation (58,59). Sleep deprivation is one of the most effective types of treatment of depression, however the effects are often short in duration, as the depressive symptoms often return with the recovery night. Great progress has been made by adding light therapy to multiple nights of sleep deprivation with recovery nights in between. Work from this thesis may be relevant to apply in chronotherapy. For instance, the fractal patterns of chapter 8, which are related to the dysfunction of the circadian rhythm, would be interesting to study before and after chronotherapy to see if the chronotherapy also has a restorative function on that marker of circadian rhythmicity. Furthermore, the discussion on optimal treatment duration and repeating the therapy multiple times are promising as well, just as we did in chapter 9 and 10 (60).

Clinical implications
The results from this thesis show that circadian disruption, sleep problems and mood symptoms are very much intertwined in patients with mood disorders, and most of all, very complex. Specifically, we show in chapter 5 that patients with bipolar disorder in a euthymic period are actually able to show a good rhythm, without more fragmentation of the rhythm than healthy controls, and show a similar synchronization to external Zeitgebers. The results from chapter 7 suggest that in the transition into a mood episode a lot is happening at the same time, but we see that specifically in manic episodes the start of the episode is preceded by sleep disturbances. Although further work is necessary to see if there are actually predicting factors within sleep and circadian variables, the feasibility of such a study as well as these pilot data are very promising. Chapter 8 shows a promising statistically defined possible biomarker, the fractal pattern, although replication is needed. Lastly, in chapter 9 and 10 we showed that patients with seasonal affective disorder can be treated successfully with only one week, instead of two weeks of light therapy, in the morning. The results showing optimal timing to the individual chronotype is not necessary for good response rates are promising, not in the least for the people responsible for the logistics behind planning and administering the light therapy.
Conclusions

From the previous chapters, we can conclude that circadian rhythm disturbances are most likely a state factor in patients with mood disorders. These disturbances, together with sleep problems play a prominent role in the transition to a mood episode in patients with bipolar disorder. Although more work is needed to fully understand this role, these disturbances might function as a predictor of upcoming transitions, enabling both patient and clinician to intervene in a timely manner. Furthermore, we showed that for a sub diagnosis of major depressive disorder, seasonal affective disorder, light therapy is very effective, and only has to be administered for a short duration, on the same time for all patients, independent of chronotype.

This thesis set out to add to the rich tradition of chronobiology within mood disorders, especially as the methods which are currently available give the opportunity to re-examine certain questions. Although this thesis shines some light on the relation between Rhythm & Blues, there are still many dark spaces to be enlightened.
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