

University of Groningen

Rhythm & Blues

Knapen, Stefan Erik

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Document Version

Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Knapen, S. E. (2019). *Rhythm & Blues: Chronobiology in the pathophysiology and treatment of mood disorders*. [Thesis fully internal (DIV), University of Groningen]. Rijksuniversiteit Groningen.

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Chapter 1

Introduction

Mood disorders are among of the leading causes for disability in the western world, with an estimated lifetime risk of about 28% (1,2). Within the spectrum of mood disorders two main disorders are major depressive disorder (MDD) and bipolar disorder (BD) (3). Since as far as a century back chronobiology, the field of biology that studies periodic (daily, monthly, yearly) phenomena, has played an important role in studying psychiatric diseases and most prominently mood disorders (27). In this thesis, a number of chronobiological mechanisms relevant for mood disorders will be studied.

Mood disorders

MDD is the most prevalent mood disorder, with a projected lifetime risk of 23.2% (2). The two core symptoms of MDD are; a depressed mood and loss of interest or pleasure in activities (3). Other symptoms include weight loss or gain, loss of energy and either insomnia or hypersomnia (box 1). A subtype of MDD is seasonal affective disorder (SAD). Patients with SAD suffer from recurring depressive episodes in a seasonal manner (4). BD has a lifetime risk of 5.2%. Patients with BD experience manic and depressive symptoms in an episodic manner (box 2). There are two subtypes of BD, bipolar disorder type I and bipolar type II. Patients with bipolar disorder type I experience at least one manic episode, defined as a period of at least one week with an elevated mood and other symptoms including racing thoughts, increased goal-oriented activities and a decreased need of sleep. Patients with bipolar disorder type II experience the same symptoms, although the symptoms are less severe, not causing significant problems in their daily life. Even under treatment 60% of BD patients experience a relapse within 2 year, and patients have residual symptoms for about a third of their lifetime (5–9).

Box 1: Symptoms major depressive disorder

1. Depressed mood most of the day, nearly every day.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
3. Significant unintentional weight loss or gain, or decrease / increase in appetite.
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 or a suicide attempt or specific plan for committing suicide.

Box 2: Symptoms manic episode

- A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least one week and present most of the day, nearly every day.
- B. During the period of mood disturbance at least three of the following symptoms:
1. Inflated self-esteem or grandiosity.
 2. Decreased need for sleep (feeling rested after a short sleep period).
 3. More talkative than usual.
 4. Flight of ideas or racing thoughts.
 5. Distractibility.
 6. Increase in goal-directed behavior
 7. Excessive involvement in activities that have a high potential for painful consequences.
- C. The mood disturbance is sufficiently severe to cause impairment in social or occupational functioning.

Rhythm and the circadian timing system

In mood disorders a number of chronobiological phenomena are clear, such as variation of mood within the day (diurnal variation), where depressed patients may experience worse mood in the morning or in the evening (28,29). Furthermore, a seasonal pattern is one of the key factors of seasonal affective disorder (4). Lastly the prominent place of sleep problems such as early morning awakening, in- and hypersomnia, in the diagnostic criteria shows the link between chronobiology and mood disorders. In both MDD and BD sleeping difficulties is a diagnostic criterion. In MDD, 60-84% of the patients experience insomnia, problems of initiating and maintaining sleep (10). In BD, one of the key components of a manic episode is the decreased need for sleep and during a depressive episode many patients experience insomnia (11). Furthermore, aside from the actual sleep duration, the timing of sleep and the daily activity (the rest-activity rhythm) is implicated in these mood disorders. Especially in BD, disturbances in this rest-activity rhythm are thought to be an underlying trait factor, present in every state of the disease.

The human rest-activity rhythm is regulated by an intrinsic clock, that steers the intrinsic circadian rhythm. The intrinsic rhythm, the rhythm that would occur if a person would have no timing cues, is 24.2 hours (14,15). The intrinsic clock is entrained daily by these outside timing cues called *Zeitgebers* (synchronizers). The adaptation of the internal circadian (circa: around, dies: day) rhythm in people is regulated by a set of neurons located in the *suprachiasmatic nucleus (SCN)* in the anterior part of the hypothalamus (16). The SCN contains a cell-autonomous transcription-translation loop of a core set of genes called the clock genes. Among these genes are *Clock*, *Bmal1*, *Per1*, *Per2*, *Cry1* and *Cry2*. The SCN regulates the rhythm in downstream targets, including brain regions that are important for the regulation of sleep, such as the ventrolateral preoptic area (VLPO) and the lateral hypothalamus (17,18). The most important *Zeitgeber* is light through the retina. This light has an effect on the SCN through retinal ganglion cells and causes a shift in the circadian rhythm (19,20). The direction of the shift depends on the time of day, with evening light causing a phase delay, while morning light causes a phase advance (21,22). Our internal clock is aligned with the outside world through this phase shifting effect of light. However, our internal clock can also be out of sync with the outside world, being misaligned with the outside world. This misalignment of the circadian rhythm is associated with a number of health problems, such as obesity and an increased cardiovascular risk profile (23,24). This misalignment not only includes the misalignment with the outside world and the internal clock, but also the misalignment of the central clock (the SCN) and the timing in other organs in the human body, such as the liver and the muscles, although this is outside of the scope of this thesis (16).

Vulnerability to mood disorders

Whether a person develops a mood disorder is the result of a multifactorial process (11,30). Finding underlying vulnerability factors for the development of mood disorders is important to increase our understanding of the pathophysiological mechanisms of the disease.

Genetic vulnerability

One of the underlying factors could include abnormalities in the molecular clock. The circadian timing system is regulated by a transcriptional-translational feedback loop constituted by clock genes (16,31). Abnormalities in these clock genes have been implicated in mood disorders. *NPAS2* has been implicated in SAD, and there might be an association with haplotypes on the core clock genes *PER3* and *ARNTL* and BD (32–34). Another indication that the core clock genes might play a role in the BD is the fact that *Clock* knock-out mice display a behavioral profile similar to a manic episode, including hyperactivity, decreased sleep and an increase in reward-seeking behavior (35). Treating these knock-out mice with lithium, the first treatment of choice for BD, seems to restore this behavior in the direction of the wild-type mice. Despite these findings, a specific genetic marker has not been found in mood disorders, and studying the genetic vulnerability alone might not be sufficient. Finding a link between genetic characteristics and psychiatric outcome might provide an interesting biomarker for clinical practice (11,30).

Chronotype and mood disorders

Another possible vulnerability factor is the person's preference for morning or evening activities, called a person's chronotype. A morning type (or 'lark') has a preference for early awakening, morning activities and an early bedtime, while the evening chronotype ('owls') have a preference for later activities. Throughout the population there is a great variety within chronotype, the evening chronotype is associated with a younger age and morning types are more common in older people and in women (36,37). Chronotype might be a non-invasive marker of internal phase, where people with a later chronotype also have a slightly longer running internal clock (internal phase longer than 24.2 hours) (14,38). Although evening types prefer their timing of activities later on the day, our society typically demands earlier activities. This misalignment results in social jetlag (39). Just as a jetlag caused by travelling across time zones, the internal phase is out of sync with the external world, and just like a jetlag from travel this can cause significant health risks. Social jetlag has been associated with obesity and an adverse cardiovascular risk profile (23,24,40). Most often people with an evening chronotype have more social jetlag. The evening chronotype is associated with MDD in a number of studies (41–47). The evening chronotype has also been proposed as a vulnerability factor for developing depression (41,48). One of the proposed mechanisms for this risk is, just as in cardiovascular risk, the social jetlag associated with the evening type.

Link between mood disorder and rhythm problems

A non-invasive method to study the circadian rest-activity rhythm is the use of actigraphy. With actigraphy people wear a wristband on their non-dominant wrist which measures movement over the day (49,50). This wristband records activity continuous-

ly and stores it on a minute-by-minute basis. Participants continue their day-to-day life, resulting in representative measures of their daily rest-activity patterns. Sleep and circadian rhythm variables can be calculated from this wrist activity data. To assess the stability and variability of the rest-activity rhythm van Someren et al. developed different non-parametric variables (51). These variables include intradaily variability, interdaily stability, activity measures during the most active 10 and most inactive 5 hours of the day and the amplitude of the rhythm (relative amplitude). These non-parametric measures provide a sensitive method applicable to wrist-activity data to describe circadian rhythmicity (51). To get a representative value for these measures, a couple of days of actigraphy is necessary, typically around 10 days or more (52). Sleep variables are assessed on a day-to-day basis and can also be derived from actigraphy data. The activity during the night, combined with a self-reported sleep log including bed- and get-up time, is used as an approximation of sleep and wake during the night (50). Although complete certainty of the sleep/wake state of a participant cannot be achieved, actigraphy is validated with the golden standard to assess sleep/wake states, polysomnography (53).

Patients with BD experience sleep and rest-activity disturbances during mood episodes. In manic episodes they experience later bedtimes, a more fragmented rhythm and a shorter sleep duration, whereas they experience less sleep efficiency, insomnia and lower activity levels during depressive episodes (11,54). However, these problems are not only implicated during mood episodes, but also arise in patients without any mood problems, i.e. patients in a euthymic phase (55–57). As these studies are typically performed in small sample sizes and with a short duration of actigraphy measurement, the question whether these symptoms are stable trait features or more a state feature of bipolar disorder, fluctuating with the episodic states, remains unsolved. If these rhythm disturbances are a trait-feature, it might be used as a biomarker, which could assist the diagnostic process to get to the diagnosis of BD. As the time from the first onset of symptoms to first treatment of BD is around 10 years, there is a dire need for diagnostic markers in BD (58).

Although the question whether rest-activity disturbances are a trait feature, or a state feature, is of interest for both diagnostic and therapeutic reasons, the interplay between sleep, rest-activity and mood disturbances is of interest for patients already diagnosed with, and thus suffering from, the disorder. Studies conducted as early as the late 70s and early 80s imply there might be a direct link between disruptions in sleep, the rhythm and the development of mood problems (59,60). When patients are asked what preceded their onset of a mood episode, 77% of the patients reported sleep disturbances as an early symptom of a manic episode, making it the most clear prodrome (early symptom of a disorder) for mania (61). For a depressed episode, 24% of the patients reported sleep disturbances as a prodrome. In a study using subjective sleep measures, in the form of a sleep diary, a mood change was preceded by a change in sleep and or bedrest duration (62). The current technological abilities make it easier to study a patient almost in real time and in their own setting. Ecological Momentary Assessment (EMA), a method of studying patient behavior in real time and in their own personal life, provides a unique opportunity to study the link between sleep and mood

problems (63). Monitoring patients with BD with fine grained ecological measurements is of great potential, especially as this can provide information on which aspects of the sleep and rest-activity rhythm precede (and might predict) mood relapses, and can also provide information when these problems may result in a full relapse. As preventing a relapse is the key goal of most interventions for BD early signals of an imminent mood episode can aid both patients and clinicians.

Fractal markers from rest-activity data in bipolar disorder

From activity data, different diagnostic markers can be derived. A relative new method to study actigraphy data is studying the *fractal pattern* of the activity rhythm. Many physiological signals, such as motor activity, show similar temporal structures on different time scales (64). The patterns are called *fractal* fluctuations and are found in many places in nature, and also in healthy human physiology (65). The loss of this fractal patterns is associated with the loss of a physiological mechanism. An example is the loss of a fractal pattern in rodent motor activity on larger time scales caused by the lesion of the SCN, the center in the brain responsible for the circadian rhythm in the body (66,67). As BD is also associated with problems in the circadian rhythm, fractal patterns, or the loss thereof, might function as a marker for BD.

Treatment of mood disorder through rhythm interventions

Circadian disturbances are not only interesting as a diagnostic marker or an episode predictor, they are also an important target point for treating mood disorders. Among different therapies, one of the more effective, with few side effects is light therapy for seasonal affective disorder (4). Since the discovery of light therapy to relieve symptoms of depression in patients with a seasonal depression, a number of studies have shown its effectiveness and it is currently the treatment of choice for SAD in the Netherlands (12,68,69). Although it is the treatment of choice, there is no consensus on the duration of the light treatment. Earlier studies show that only one week of light therapy is enough to relieve and prevent depressive symptoms during the rest of the winter season (70). Other protocols typically use 8 weeks, or even advise to use light therapy until the beginning of the spring (71). Alongside the duration of the light therapy, the timing of light therapy is topic of discussion. Especially as one of the hypotheses of the treatment effect is dependent on the phase shifting properties of light in the morning (72–74). Current protocols advise to time the light therapy to a person's chronotype, with earlier light for morning chronotypes and later light for patients with evening chronotypes (71). Other studies argue against this phase shift hypothesis and suggest that, although light in the morning is needed, timing exactly to a chronotype might not be necessary (17,75,76).

Thesis outline

Although sleep and rest-activity disturbances are primarily found during symptomatic states of mood disorders, these disturbances can also pose a vulnerability to the development of the disease. Furthermore, the interplay between rest-activity disturbances and the development and the course of mood disorders is of interest. In this thesis different studies are described that have been conducted to investigate genetic risk factors, disturbances in the rest-activity rhythm, and the treatment of mood disorders, all with the aim to better understand the relation between rhythm and blues.

The first part of this thesis (chapter 2-4) will focus on vulnerability factors for mood disorders within chronobiology by studying epidemiological data from the Netherlands Study of Depression and Anxiety (NESDA). First, we study the relation between circadian genes, chronotype and mood disorders, to see if **there might be an underlying genetic predisposition for mood disorders within circadian genes** (chapter 2). Furthermore, we aim to answer the question if this genetic vulnerability is mediated through the chronotype of the patients. Next, **we study whether social jetlag, associated with the evening chronotype, is actually related to MDD**, as it is often hypothesized (chapter 3). In chapter 4 **we discuss the problems with studying chronotype in patients who show different behavior in different mood states**.

The second part of this thesis (chapter 5-8) focuses specifically on BD and actigraphy measures within this disease. In this part, the link between rest-activity disturbances and mood within the different stages of the mood disorder will be studied. We study circadian measures in euthymic patients, to see if **patients with BD show circadian rhythm disturbances in the euthymic phase of the disease compared to controls** (chapter 5). Next, **we study if rest-activity patterns can function as an early warning signal of imminent mood changes in a single subject** (chapter 6). In chapter 7 **we study the temporal relation between sleep and circadian disturbances and mood in the onset of a mood episode**. In chapter 8 we show another measure we can obtain from actigraphy data, **fractal patterns, to see if they could function as a marker for BD**.

The third and last part of this thesis focuses on the treatment side of mood disorders. In a combined sample of different studies studying light therapy effects within SAD **we looked at the duration of light therapy** (chapter 9) and **the timing of light therapy** (chapter 10). In the last chapter of this thesis I will discuss our findings in a broader context (chapter 11).

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