CHAPTER 1

General background
and thesis overview
INTRODUCTION

Life on earth is subjected to geophysical cycles that result in the alternation of light and darkness and the change of seasons. Virtually all species are physiologically adapted to these regular changes in the environment by means of an endogenous timekeeping mechanism. In mammals this biological clock is localized in the suprachiasmatic nuclei (SCN) of the brain (Van Esseveldt et al 2000). The biological clock generates endogenous physiological rhythms with a near-24-hour period and is therefore also referred to as the circadian pacemaker (‘circadian’ is derived from the Latin words *circa* which means ‘approximately’ and *dies* which means ‘day’). By its sensitivity to light, the circadian pacemaker synchronizes these near-24-hour oscillatory processes with the 24-hour environmental light-dark cycle. Thus, the circadian pacemaker ensures optimal functioning with respect to the time of day. Furthermore, by the ability of measuring day length (or photoperiod), i.e., the time period between sunrise and sunset, the circadian pacemaker also triggers seasonal behavior in animals, such as hibernation and migration. In humans, seasonal behavioral rhythms have been described in for instance the rates of conception, mortality and suicides (Aschoff 1981). Nevertheless, whether these seasonal behavioral rhythms in humans originate from the influence of the circadian pacemaker, the geophysical and social environment or an interaction of both still remains to be established.

The earliest description of circadian rhythms probably dates back to the fourth century BC when Alexander the Great observed the daily changes in the orientation of the leaves of plants (Dietzel 1990). However, the circadian plant movements were not considered as governed from within but rather as a passive response to the environment. The first report on the continuation of these daily rhythms in plants in the absence of environmental stimuli was published in 1729 by the French astronomer D’Ortous de Mairan who reported on the daily movements of the *Mimosa pudica* in constant darkness (Dietzel 1990). It was not until the 20th century, however, that endogenous circadian rhythms were observed in humans isolated from environmental influences and time-cues (Aschoff and Wever 1962). While living in an underground bunker, nine subjects showed rest-activity cycles of approximately 25 hours. Recently, more sophisticated studies have shown that the endogenous circadian rhythms in humans actually exhibit a period very near to 24 hours (Czeisler et al 1999).

The majority of geophysical influences on daily life appears to have been attenuated by means of modern technology. On the other hand, it is modern society that confronts humans with their chronobiology. The fast passage of several time zones by air traveling results in a desynchronization of the endogenous circadian rhythms.
with the environmental light-dark cycle. As a consequence, after long-distance west- or eastbound flights, many travelers experience symptoms of jetlag, such as fatigue, sleeping problems, loss of concentration and gastrointestinal disturbances (Waterhouse et al 1997). Likewise, the dissociation between the environmental light-dark cycle and the endogenous circadian rhythms caused by shift work gives rise to similar complaints (Eastman et al 1995).

A diurnal variation in mood (i.e., an improvement of mood over the course of the day), a temporal alleviation of symptoms by the deprivation of sleep and disturbed sleep patterns are often observed in major depressed patients. These clinical features gave rise to several hypotheses concerning the involvement of either the circadian pacemaker, a sleep-wake cycle dependent process or an interaction between these two in the pathogenesis of mood disorders (reviewed in for example Van den Hoofdakker 1994; Wirz-Justice 1995; Buysse et al 1999; Wirz-Justice and Van den Hoofdakker 1999; Boivin 2000).

Hypotheses about the involvement of a circadian pacemaker related process in depression have especially gained interest for winter-type Seasonal Affective Disorder (SAD). SAD or winter depression is characterized by the annual recurrence of depressive symptoms in the winter season and a complete absence of these symptoms in spring and summer (Rosenthal et al 1984). Remarkably, the majority of SAD patients can be effectively treated with bright light (Terman et al 1989). Similar to non-seasonal depressives, SAD patients often show diurnal mood variations (Graw et al 1991; Krauss et al 1992), disturbed sleep patterns (Anderson et al 1994) and an improvement of mood after sleep deprivation (Graw et al 1998). Since the circadian pacemaker is sensitive to light and may function as a regulator of annual rhythms, the seasonality of symptoms and the efficacy of bright light therapy have particularly linked the pathogenesis of SAD to disturbances of the circadian pacemaker.

Hypotheses about the pathogenetic role of an abnormal sleep-wake cycle related or circadian pacemaker related process have offered a tempting theoretical framework for the explanation of both seasonal and non-seasonal affective disorder. Nevertheless, up till now research did not provide consistent support for these hypotheses. Yet, the design of most of these previous studies has often not been entirely suitable for the testing of chronobiological theories. The present thesis is devoted to the testing of some of the chronobiological theories in winter-type Seasonal Affective Disorder. The studies described used one of the most appropriate protocols currently available.
THE PHYSIOLOGY OF THE CIRCADIAN SYSTEM

In mammals, the circadian rhythms shown in a variety of processes are probably all
governed by one circadian pacemaker seated in the suprachiasmatic nuclei (SCN) of
the hypothalamic area in the brain (Miller et al 1996; Murphy and Campbell 1996; Van
Esseveldt et al 2000). This brain area is localized above the crossing of the optic ner-
ves (optic chiasm). Definite proof for the SCN as the locus of the ‘circadian master
clock’ has been provided by transplantation experiments in hamsters showing diffe-
rent cycle lengths of their circadian rhythms. The circadian rhythms of the host ham-
sters were first eliminated by the ablation of their SCN. After the subsequent trans-
plantation of SCN grafts, circadian rhythms of the arrhythmic hamsters were restored
and displayed a cycle length similar to those of the donor hamsters (Ralph et al 1990).

The SCN receives its main input from the retina via the retino-hypothalamic tract, and from the intergeniculate leaflet of the lateral geniculate nucleus via the
geniculo-hypothalamic tract. The SCN, in turn, projects to the subparaventricular zone and the dorsomedial nucleus of the hypothalamus and to the paraventricular nucleus of the thalamus (Van Esseveldt et al 2000). The efferent pathways are invol-
ved in the regulation of the circadian modulation of physiology and behavior. One of
them leads via the superior cervical ganglion to the pineal gland (Miller et al 1996).
The pineal gland produces the hormone melatonin, which is involved in the commu-
ication of circadian time to other organs. The secretion of melatonin exhibits a 24-
hour periodicity and predominantly takes place during darkness in both nocturnal
and diurnal animals.

The Synchronizing Effects of Ocular Light

The circadian pacemaker synchronizes the endogenous circadian rhythms both rela-
tive to each other and to the exogenous 24-hour day. The latter synchronization is cal-
led entrainment. Endogenous circadian rhythms are entrained to the 24-hour day by
means of the ability of the pacemaker to react to certain environmental stimuli, or
Zeitgebers (meaning ‘time-givers’). The environmental light-dark cycle is the most
important Zeitgeber of the circadian system of both animals and humans. Nonphotic
stimuli (such as food availability, forced activity and social cues) are also involved in
the entrainment of the mammalian circadian system, but they have to be considered
as comparatively weak synchronizers (Murphy and Campbell 1996, Klerman et al

Studies in healthy human subjects have shown that retinal light exposure sup-
presses the nightly production of melatonin by the pineal gland (Lewy et al 1980).
Furthermore, it synchronizes the various circadian rhythms to the environmental
light dark cycle throughout the day (Jewett et al 1997) in a dose-dependent manner.
Boivin et al. (1996). The direction and the magnitude of the resulting shift of the circadian pacemaker are dependent on the timing of light exposure. Light before the circadian temperature minimum (which occurs in the early morning) causes a phase delay of the circadian pacemaker (i.e., schedules it later in time), whereas a phase advance (i.e., a shift to an earlier time) can be obtained by light exposure after this minimum (Honma and Honma 1988; Minors et al. 1991). In a phase response curve (PRC) the phase shifts are plotted as a function of the circadian time of light exposure. Figure 1.1 presents the PRC for diurnal animals (Beersma et al. 1999). In this graph circadian time zero (CT0) represents the habitual time of awakening under normal conditions.

**The Effects of Extraocular Light**

It is generally believed that adult mammals lack the capacity for extraretinal circadian photoreception (Underwood and Groos 1982). The recent findings of Campbell and Murphy (1998) challenged that notion about the (human) circadian system. In their provocative study in healthy humans, extraocular light pulses were applied to the skin of the bend of the knees (i.e., the popliteal fossae). Like ocular light, these extraocular light pulses induced phase shifts of the circadian temperature and melatonin rhythms (Campbell and Murphy 1998). Furthermore, the phase response curve computed from this extraocular light experiment resembled that resulting from ocular light pulses. Unfortunately, results of other groups raised doubts about the extraocu-

![Figure 1.1](image.png)

**Figure 1.1** Phase response curve of diurnal animals, such as humans. Depending on the circadian time of light exposure, the circadian pacemaker shifts to an earlier time (phase advance) or a later time (phase delay). Circadian time zero (CT0) represents the habitual time of rising under normal conditions. (From Beersma et al. 1999)
lar photoreception of the circadian pacemaker. Neither studies performed in healthy subjects by other groups (Lindblom et al 2000a, 2000b; Eastman et al 2000), nor studies in hamsters (Meijer et al 1999; Yamazaki et al 1999) provided results consistent with those of Campbell and Murphy (1998). And unlike ocular light, extraocular light was demonstrated to be incapable of directly suppressing the nightly secretion of melatonin (Lockley et al 1998; Hébert et al 1999; Jean-Louis et al 2000).

HUMAN CIRCADIAN RHYTHM RESEARCH

In human circadian rhythm research, the circadian variation of core body temperature and melatonin are often used as markers of pacemaker output. However, the interpretation of these measures in terms of circadian output is complicated by several masking factors. One such masking factor is light. The nightly secretion of melatonin can be directly suppressed by light exposure (Lewy et al 1980). Therefore, the most accurate estimates of circadian pacemaker characteristics derived from the melatonin secretion profile are obtained in dim light. Another important masking factor is the sleep-wake cycle. Sleep, activity and meals strongly modify body temperature. The endogenous circadian contribution to temperature data can be obtained by experimentally controlling for masking factors in a constant routine- or a forced desynchrony protocol.

Constant Routine Studies

In a constant routine procedure masking factors are minimized by keeping subjects in a supine posture, feeding them with frequent small meals, and exposing them to a prolonged period of wakefulness (Mills et al 1978; Czeisler et al 1985). Under these controlled conditions, circadian amplitude and phase can be accurately determined from for instance core body temperature recordings. However, the sleep deprivation induced by the constant routine procedure elicits a worsening of mood in healthy subjects (Brendel et al 1990) and an improvement of mood in depressed patients (Graw et al 1998). Therefore this procedure has limitations for the study of mood regulation.

Forced Desynchrony Studies

The forced desynchrony (FD) protocol enables control over the relevant masking factors without eliminating them, while sleep deprivation effects are avoided. During FD participants are subjected to a sleep-wake cycle which is either shorter or longer than 24 hours, i.e., either 20 hours or 28 hours. These subjective days are spent in dim light (<10 lux) and have a fixed temporal structure. The circadian pacemaker is not able to follow this unusual alternation of wakefulness and sleep and starts to oscillate according to its own period (Klerman et al 1996). Consequently, the pacemaker and the sleep-wake cycle desynchronize and in the course of time the scheduled
activities and sleep periods occur at all endogenous circadian phase positions (Kleitman and Kleitman 1953; Czeisler et al 1986; Dijk et al 1992). Thus, the contributions of the sleep-wake cycle and the pacemaker to circadian modulating variables can be disentangled by means of a mathematical method (Dijk et al 1992; Hiddinga et al 1997), without the need for prolonged sleep deprivation. An example of an FD protocol is depicted in Figure 1.2.

FD protocols in healthy subjects have shown circadian and sleep-wake dependent influences on core body temperature (Hiddinga et al 1997; Czeisler et al 1999). Moreover, a complex interaction between these two components has been demonstrated in many respects: the production of melatonin (Wyatt et al 1999), the regulation of sleep (Dijk and Czeisler 1995; Wyatt et al 1999), and the regulation of subjective alertness, cognitive performance (Dijk et al 1992), and mood (Boivin et al 1997). The circadian variation of alertness, performance and mood was found to be closely associated with the circadian oscillation of core body temperature (Dijk et al 1992;

**Figure 1.2** Double plot of a 120-hour forced desynchrony protocol in which subjects are subjected to six 20-hour days. On the vertical axis the number of days in the protocol is plotted and the horizontal axis represents time of day in hours. The waking periods are represented by the open spaces, whereas the open boxes indicate the periods for sleep. The open circles depict the moments at which subjects have to perform psychometric tests. This overview shows a 10-day protocol. The black circles indicate the start and end of the forced desynchrony protocol respectively. The first 4 days of the protocol consist of baseline days at home in which subjects adhere to a regular sleep-wake schedule. During these days sleep is only allowed between midnight and 8 AM. After a habituation period in the lab, subjects are scheduled on six 20-hour subjective days in dim light. The circadian pacemaker cannot adapt to this rapid alternation of wakefulness and sleep and starts to ‘free-run’ according to its own period. Consequently, in the course of time the sleep-wake cycle scans through all circadian phases. Subsequently, pacemaker and the sleep-wake cycle-related contributions to the variation of variables under study can be disentangled mathematically.
Boivin et al 1997). An improvement and worsening was observed with the ascending and descending limbs of the endogenous circadian temperature curve, which reaches its minimum in the early morning. Additionally, alertness, performance and mood were found to gradually deteriorate with the duration of prior wakefulness. Thus, the circadian pacemaker counteracts the deterioration of alertness, performance and mood in the course of wakefulness and provides a consistent level of these processes throughout the habitual period of wakefulness.

**AFFECTIVE DISORDERS AND CIRCADIAN RHYTHMS**

From ancient times up to the present, the relationship between physiological rhythms and health has been recognized. The Hippocratic works of the fifth and fourth century BC outlined the humoral theory that was based on the connections between man and his environment (Roccatagliata 1986). According to this theory, four 'bodily fluids' or *humors* govern human physiology: blood, yellow bile, black bile and phlegm. Depending on the time of year, one of these humors predominates and can give rise to a particular set of diseases. Ancient scientists postulated the existence of an internal timing mechanism that regulates all kinds of rhythms. Aristotle (384-322 BC) for instance taught that the *sensus communis*, i.e., 'the organ that synthesizes all perceptions' governs biological rhythms such as those of sleep and wakefulness (Roccatagliata 1986). According to Aretaeus of Cappadocia (ca. 150 BC), the *vis vitalis*, or 'vital tone', which is seated in the heart, shows circadian rhythmicity. He taught that an inversion of the vital tone's circadian rhythm causes the sudden awakenings and great tiredness often observed in melancholic patients (Roccatagliata 1986). Much later, Descartes (1596-1650) assumed that bodily functions are regulated by a clock and attributed a clock-like function to the pineal gland (Barrera-Mera and Barrera-Calva 1998). Today, chronobiology has become an important discipline in the study of somatic and mental functioning.

**Chronobiological Theories for Depression**

Some clinical characteristics of depression hint at a possible involvement of disturbances of chronobiology in the pathogenesis of this disorder. Depressed patients often complain of sleep disturbances, such as difficulties falling asleep, increased wakefulness during the sleeping period and early morning awakenings (Benca et al 1997). Moreover, a temporal alleviation of symptoms after deprivation of sleep has often been observed in major depression and winter-type Seasonal Affective Disorder (Wirz-Justice and Van den Hoofdakker 1999).

The two-process model of sleep regulation describes how sleep is regulated by the interaction of a sleep-wake cycle dependent process S and a circadian pacemaker rela-
ted process C (Borbély 1982; Daan et al 1984). Not surprisingly, the above mentioned clinical features of depression gave rise to chronobiological theories concerning the involvement of either process C, process S, or an interaction between these two processes in the dysregulation of mood (reviewed in for example Wirz-Justice 1995; Wirz-Justice and Van den Hoofdakker 1999; Boivin 2000). With respect to process C, it has been suggested that, for instance, an abnormality of circadian phase relative to the timing of the sleep-wake cycle or a blunted circadian amplitude were involved in the pathogenesis of depression. Along similar lines, a disturbance of process S, i.e., a deficiency in the homeostatic buildup of sleep pressure, has also been proposed to underlie the pathogenesis of affective disorders. Many studies have been performed to verify these chronobiological hypotheses for depression. However, up till now they lack consistent empirical support.

**Seasonal Affective Disorder and Circadian Pacemaker Disturbances**

Winter-type Seasonal Affective Disorder (SAD), or ‘winter depression’, is a depressive syndrome that is distinguishable from other types of affective disorder by its clinical course and symptom profile (Rosenthal et al 1984; American Psychiatric Association 1994). The symptoms of SAD annually recur in autumn and/or winter and are completely absent in spring and summer. Those cases of seasonal depression in which seasonal psychosocial stressors are involved are excluded from this diagnosis. Apart from common depressive complaints, such as sadness, loss of interest in daily activities and of the ability to concentrate, SAD is often marked by prominent ‘atypical’ symptoms. These symptoms are less frequently observed in non-seasonal types of depression and include fatigue, hypersomnia, an increase of appetite (especially for carbohydrates) and weight gain. Another prominent feature of SAD is that the majority of patients can be effectively treated by the ocular exposure to bright light (Terman et al 1989). Not surprisingly, the seasonality of symptoms and the beneficial effects of light therapy have led to hypotheses concerning the involvement of the circadian system in SAD. These circadian hypotheses have focussed on the timing of the circadian rhythms with respect to the environmental light-dark cycle as well as on possible abnormalities of the circadian rhythm per se. Figure 1.3 shows a schematic representation of a circadian rhythmic process. Circadian rhythm research is concerned with possible abnormalities in circadian period, phase or amplitude.

**Photoperiod Hypothesis**

In the first description of SAD (Rosenthal et al 1984) a parallel was drawn between this disorder and hibernation observed in animals. It was suggested that SAD results from the shortening of day length (or photoperiod) during the winter months. However, a study in which light therapy strategies were compared that simulated either a short or long photoperiod showed that both were effective in the treatment of
SAD (Wehr et al 1986). Furthermore, later studies also strongly suggest that day length is not an important or crucial factor in the treatment of SAD (see for instance Wirz-Justice et al 1993; Meesters et al 1995).

**Phase Shift Hypothesis**

The phase shift hypothesis postulates that a phase delay of the circadian pacemaker relative to the timing of the habitual sleep-wake cycle underlies the pathogenesis of SAD and that the phase-advancing properties of morning light account for the efficacy of light treatment (Lewy et al 1987a). While some authors have shown morning light to be superior (Lewy et al 1998; Terman et al 1998), others have found no difference between the effects of light applied in the early morning and light applied at other times of the day (Wirz-Justice et al 1993; Meesters et al 1995).

**Amplitude Hypothesis**

According to the amplitude hypothesis a blunted circadian amplitude underlies the pathogenesis of SAD. The amplitude-enhancing effect of light applied in daytime might explain the beneficial effects of light treatment (Czeisler et al 1987).

**Empirical Evidence for Circadian Pacemaker Disturbances in SAD**

Several studies have been performed to assess the functioning of the circadian pacemaker in SAD patients. However, the data obtained in these studies do not yield a

---

**Figure 1.3** From this schematic representation of a circadian-modulating process a period, phase and amplitude can be discerned. The nadir and acrophase represent the circadian phase at which the minimum and maximum of the circadian rhythm is reached. The nadir is often arbitrarily regarded as the starting point of the circadian rhythm.
coherent picture. The reason for the discrepancies might be that the data are contaminated by several masking factors. Constant routine (CR) studies experimentally control for masking factors. So far, two CR studies have been performed in female SAD patients and matched controls. In both studies, certain characteristics of the circadian rhythm of body temperature (Dahl et al 1993; Wirz-Justice et al 1995) melatonin levels (Dahl et al 1993) and cortisol levels (Avery et al 1997) were found to be phase-delayed in patients compared with those measured in controls. After light therapy, a phase advance of some of the circadian temperature characteristics (Dahl et al 1993; Wirz-Justice et al 1995) and of the secretion of melatonin was observed (Dahl et al 1993). Both studies did not reveal disturbances of circadian amplitude, nor did the amplitudes change significantly in response to treatment. However, the CR induced sleep deprivation affects mood in both healthy subjects (Brendel et al 1990) and depressed patients (Graw et al 1998). Therefore, in the present thesis circadian pacemaker characteristics were studied by means of a forced desynchrony protocol. As argued before, this protocol allows the study of the circadian pacemaker without the need for prolonged sleep deprivation.

Outline of the Studies Presented in this Thesis

The aim of the present project was to study the possible involvement of chronobiological disturbances in SAD.

The thesis starts with an historical chapter. Throughout all ages, the importance of the seasons for the etiology and pathogenesis of several illnesses and the beneficial properties of both sun and artificial light with respect to preservation and restoration of health have been recognized. Since they were first described in the early 1980s, SAD as well as its treatment with light may seem to represent brand new findings. However, a review of history reveals a different picture. In chapter 2, the history of the opinions on seasonality of affective disorders and the efficacy of light in its treatment is reviewed. This overview puts the present thesis as well as previous research on SAD in a historical perspective and shows that ancient knowledge might still contain opinions that are valuable for modern medical science.

Because of the large response rate, bright light therapy has become the treatment of first choice for SAD (Terman et al 1989). It has been suggested that the circadian pacemaker is phase-delayed in SAD and that morning light therapy is beneficial for this disorder through its phase-advancing properties. However, the definite proof of this suggestion is still lacking due to the inherent problem that the perfect placebo treatment for light therapy does not exist.

As mentioned earlier, Campbell and Murphy published a remarkable new finding. They reported that, like ocular light, extraocular light is capable of inducing phase shifts of the human circadian pacemaker (Campbell and Murphy 1998). We argued
that, if this finding were valid, it would offer the possibility to assess the therapeutic potency of light in a genuine double-blind placebo-controlled protocol. The study is described in chapter 3. SAD patients received either extraocular light by fiber-optic illumination or placebo (no light) in the popliteal fossae. Neither patients nor staff knew whether light was actually applied or not. It was found that the response to extraocular light therapy in SAD patients did not exceed the placebo effect. Moreover, extraocular light did not induce a phase shift of the circadian pacemaker.

To test the chronobiological theories for the pathogenesis of SAD, patients were subjected to a 120-hour forced desynchrony protocol during a depressive episode, while recovered upon light treatment, and in summer. For comparison, also healthy matched control subjects underwent the same protocol in winter and summer. In chapter 4 the analysis of data on core body temperature and melatonin is described. The endogenous circadian period, phase and amplitude were the object of study (see Figure 1.3). The endogenous circadian period was computed from the melatonin data and subsequently integrated in the analysis of the phase and amplitude of the endogenous circadian temperature rhythm. The comparison between patients and controls and between the various conditions to which they were subjected revealed that the circadian pacemaker characteristics are similar in SAD patients and controls. Therefore, it is concluded that process C is undisturbed in SAD.

Many SAD patients complain of hypersomnia and daytime drowsiness. Since human sleep is regulated by the interaction of circadian and homeostatic processes, sleep disturbances may be due to either one of these factors. In chapter 5, the data on polysomnographically recorded sleep, obtained in the same forced desynchrony protocol are described. Because the analysis of core body temperature data revealed no disturbance of process C, this analysis focuses on process S related aspects of sleep regulation in SAD. No abnormalities in the sleep stage parameters, the relative power spectra and the time course of power in various frequency bands across the first three NREM-REM cycles were observed. The data therefore suggest that also process S is undisturbed in SAD.

In healthy subjects, both the duration of wakefulness (process S) and the circadian pacemaker (process C) have been demonstrated to modulate mood. In chapter 6 the sleep-wake cycle related and pacemaker-related contributions to the modulation of mood are examined in SAD. The impact of the pacemaker and the sleep-wake cycle on the regulation of mood appeared to be substantial but very similar in patients and matched controls.

Finally in chapter 7, a general discussion of all studies described in this thesis is presented.