Sleep Medicine Reviews (2007) 11, 485–496

SLEEP MEDICINE reviews

www.elsevier.com/locate/smrv

CLINICAL REVIEW

Circadian rhythm sleep disorders: Characteristics and entrainment pathology in delayed sleep phase and non-24 sleep–wake syndrome☆

Masako Okawa[a,*], **Makoto Uchiyama**[b]

[a]*Department of Sleep Medicine, Shiga University of Medical Science, Otsu, Japan*
[b]*Department of Psychiatry, Nihon University School of Medicine, Tokyo, Japan*

KEYWORDS
Non-24-h sleep–wake rhythm;
Delayed sleep phase syndrome;
Light therapy;
Melatonin;
Body temperature;
Depression;
Sleep homeostasis

Summary This paper presents a clinical review of delayed sleep phase syndrome (DSPS) and non-24-h sleep–wake syndrome (non-24). These syndromes seem to be common and under-recognized in society, not only in the blind, but also typically emerging during adolescence. Both types of syndrome can appear alternatively or intermittently in an individual patient. Psychiatric problems are also common in both syndromes. DSPS and non-24 could share a common circadian rhythm pathology in terms of clinical process and biological evidence. The biological basis is characterized by a longer sleep period, a prolonged interval from the body temperature nadir-to-sleep offset, a relatively advanced temperature rhythm, lower sleep propensity after total sleep deprivation, and higher sensitivity to light than in normal controls.

There are multiple lines of evidence suggesting dysfunctions at the behavioral, physiological and genetic levels. Treatment procedures and prevention of the syndromes require further attention using behavioral, environmental, and psychiatric approaches, since an increasing number of patients in modern society suffer from these disorders.

Introduction

The sleep–wake rhythm in humans is regulated by the circadian timing system, and disorders of this system are known as circadian rhythm sleep disorders (CRSD), which can have multiple etiology but result in maladjustment of the biological clock with respect to the environment. Persons suffering from these sleep disorders develop an inability to

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASPS, advanced sleep phase syndrome; BT, body temperature; CRSD, circadian rhythm sleep disorder; DSPS, delayed sleep phase syndrome; M-E, morningness-eveningness; Non-24, non-24-h sleep–wake syndrome; NOS, not otherwise specified; PRC, phase response curve

☆Dedicated to Anna Wirz-Justice in recognition of her contributions to the field made during her career at the Psychiatric University Clinics Basel.

*Corresponding author. Tel.: +81 77 548 2915; fax: +81 77 548 2991.
E-mail address: okawa@belle.shiga-med.ac.jp (M. Okawa).

1087-0792/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.smrv.2007.08.001

fall asleep at the desired time at night and to wake up at the desired time in the morning. They usually force themselves to adjust to the environmental light–dark (or social) cycle, but are not often successful and may develop physical and psychological complaints during waking hours, i.e. sleepiness, fatigue, headache, decreased appetite, or depressed mood.

Patients with CRSD often have difficulty maintaining ordinary social lives, and some of them lose their jobs or fail to attend school. There has been an increasing awareness of persistent CRSDs. In our 24-h society, under conditions that may disrupt normal day–night activities, such as shift work, transmeridian flight, or exposure to bright light late at night, desynchronization of circadian rhythms can occur, resulting in CRSD.

The pathophysiology or pathogenesis of CRSD has not been fully elucidated and it cannot be subsumed under a single disorder. The syndrome is thought to be multifactorial: social, psychological, and environmental factors as well as biological factors have all been proposed to play important roles in the onset and development of symptoms, but no single factor is sufficient to explain it.

This review focuses on clinical studies of delayed sleep phase syndrome (DSPS) and non-24 h sleep–wake rhythm (non-24), which are representative syndromes in CRSD, from the viewpoints of prevalence, comorbidity, treatment strategies and pathophysiology, and proposes future research directions.

Classification of circadian rhythm sleep disorders

Circadian rhythm sleep disorders can be divided into two major groups (1): those occurring when the physical environment is altered relative to internal circadian timing (e.g. shift work, jetlag); and (2) those occurring when the circadian timing system is altered relative to the external environment (e.g. delayed sleep phase syndrome, non-24, advanced sleep phase syndrome, irregular sleep–wake rhythm). The general criteria for CRSD in the International Classification of Sleep Disorders (ICSD)[1] are defined in Table 1.

Table 1 General criteria for circadian rhythm sleep disorder.

A. There is a persistent or recurrent pattern of sleep disturbance due primarily to one of the following:
 i. Alterations of the circadian timekeeping system.
 ii. Misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep.
B. The circadian related sleep disruption leads to insomnia, excessive daytime sleepiness, or both.
C. The sleep disturbance is associated with impairment of social, occupational, or other areas of functioning.

Delayed sleep phase syndrome (CRSD, delayed sleep phase type)

Delayed sleep phase syndrome is caused by an abnormally delayed circadian clock.[2] Sleep onset and wake-up times are both significantly delayed in comparison with conventional sleep–wake times. Typically, patients with DSPS do not get sleepy until the early morning hours, and then sleep until the late morning or early afternoon. In addition to their delayed sleep period, a variety of circadian rhythms such as plasma melatonin, urinary melatonin metabolite excretion, and core body temperature have been reported to be significantly delayed in patients with DSPS.[3–6] DSPS patients are often characterized as ''night owls'', and when tested with chronotype questionnaires to determine morningness and eveningness, they score on the eveningness end of the scale. Once asleep, provided they are allowed to sleep at their own selected times, they will have normal quality sleep with normal sleep architecture, which will last for a normal time unless it is interrupted by external disturbances.[2] The continuing mismatch between the daily schedule required by the social environment and the individual's circadian sleep–wake pattern creates major social, work, and academic problems. This discrepancy has been given the appropriate and pictorial name of ''social jet lag''.[7] Sometimes DSPS patients complain of headache, loss of appetite, depressed mood, and loss of concentration. These symptoms could be caused by forced awakening in the morning to adjust their daily lives to social demands.

Evening-type individuals and patients with DSPS share many similar characteristics.[8] However, it is still unclear whether extreme evening-type and DSPS individuals share a common pathology or lie on a continuum. Several published investigations of early and late chronotypes have provided new perspectives on circadian and homeostatic regulation, which are important for addressing the nature of DSPS.[9–15]

Non-24-h sleep–wake syndrome (CRSD, free-running type, non-entrained type, hypernychthemeral syndrome)

Non-24 has been reported to be a rare condition characterized by a chronic steady pattern of about 1-h delays in spontaneous sleep onset and wake-up times in individuals living under normal environmental conditions. It occurs because the intrinsic circadian pacemaker is no longer entrained to a 24-h period and is free running with a non-24-h period, usually slightly longer than 24 h. Because most individuals are usually required to maintain a regular sleep–wake schedule, the clinical picture is of periodically recurring problems with sleep initiation, sleep maintenance, and rising, as the circadian cycle of wakefulness and sleep propensity moves in and out of synchrony with a fixed sleep period time.

Most individuals with non-entrained circadian rhythms are totally blind[16–22] and the failure to entrain circadian rhythms is related to the lack of photic input to the circadian pacemaker. Although the disorder has been considered rare in sighted people, it has been reported to occur in such individuals,[23–34] and most studies of such patients have been individual case reports. Affected patients have not usually been previously properly diagnosed and treated. Social and behavioral factors may contribute to its development. Hayakawa et al.[35] conducted a large-cohort study of sighted patients suffering from non-24, which indicated that, as well as DSPS, the disorder is not rare in individuals in their teens and 20s. This study provided important information on clinical characteristics, which will be discussed later.

Prevalence of CRSD

Although no study has systematically investigated all age groups, the incidence of DSPS has been found to be low in the general population in Japan: 0.13% among all individuals aged 15–54 years.[36] In adolescents, DSPS is reportedly a common cause of insomnia.[37–39] In Norway, 0.17% of DSPS cases were found in an epidemiological study of CRSD.[40] In Japan, symptoms in half of all adult patients with DSPS begin in childhood or adolescence,[41] and may be triggered by a long vacation (day–night reversal) or by exhausting preparation for university exams. The number of cases of DSPS and related disorders seems to have increased in the last few decades, due to many aspects of modern life such as watching TV, playing computer games, or night work, all resulting in a delay of sleep onset time.[42,43] Some of the individuals affected in this way show clear symptoms of DSPS. The frequency of DSPS patients presenting at sleep disorder clinics has been reported to be 6.7–16%.[2,44] Many of these patients seem to have an unsatisfactory and low quality of life.

Dagan and Eisensterin[45] found that among 322 patients with CRSD, 84.6% had DSPS and 12.3% had non-24. Yamadera et al.[41] reported 90 cases (74%) of DSPS and 13 cases (11%) of non-24 among 121 cases of CRSD. Kamei et al.,[46] in an intensive follow-up study of 90 CRSD patients, reported that 64 (71%) had DSPS, and 21 had non-24 (23%). All these reports suggest that DSPS is the most common syndrome in patients with CRSD.

Treatment strategies

Light therapy

It is well accepted that exposure to bright light can dramatically influence both the amplitude and phase of human circadian rhythms, and there is growing evidence that light may affect human physiology and behavior through non-circadian mechanisms as well.

In humans and other mammals, the daily light–dark cycle is a major synchronizer responsible for entrainment of circadian rhythms to the 24-h day, and phase response curves (PRC) to light have been obtained.[47–49] Since in healthy subjects the minimum core body temperature occurs approximately 1–2 h before the habitual time of awakening, the most sensitive phase of PRC to light coincides with sleep, and the timing of the monophasic sleep–wake cycle itself is a major determinant of light input to the pacemaker. Exploiting these responses of the human PRC to light, light therapy for CRSD has been carried out.

Morning bright-light therapy should be applied during the phase-advance period of the PRC, starting with immediate treatment upon spontaneous awakening for several days, advancing the treatment time in increments of about 15–30 min, and applying the treatment for several days at each new time. When the desired wake-up time has been achieved, morning light treatment should be maintained at this constant time.

These procedures are based on findings of previous research. In a clinical setting, there are many limitations to these idealized methods. Further investigations of potentially beneficial approaches should be carried out systematically with respect to light intensity, timing and duration of light exposure. Ideally, for chronobiological treatments of CRSD, individual evaluation of biological clock time is needed. This can be estimated by measuring the dim light melatonin onset (DLMO)[50] in plasma or saliva. Since this is not always possible before treatment begins, indirect information of body clock time can be rapidly estimated using the (corrected) mid-sleep time as elucidated in the Munich Chronotype Questionnaire[7] (see Roenneberg et al., this issue).

Melatonin treatment

The pineal hormone melatonin manifests a marked circadian rhythm, opposite in phase to the core body temperature rhythm. The general pattern of the PRC to melatonin suggests a near mirror image of the PRC to light: melatonin administered in the early evening induces a phase-advance, and in the early morning, a phase-delay. The circadian phase-shifting properties of melatonin have been applied to several clinical disorders, such as non-24 blind patients with CRSD.[51–60]

Sighted patients with non-24 or DSPS have also been treated successfully by melatonin administration.[61–65] For these disorders it is important to know DLMO before the start of melatonin treatment.[62,63] Melatonin treatment is most effective if administered 5 or 6 h before DLMO.[64] Furthermore, timing correctly according to DLMO may predict the efficacy of melatonin treatment in childhood DSPS.[65]

The efficacy of melatonin for DSPS has been confirmed by placebo-controlled studies.[66–68] Kayumov et al.[68] reported the efficacy of 5 mg of melatonin for some symptoms of DSPS, as confirmed by both objective and subjective measures, in a randomized, double-blind, placebo-controlled crossover study. However, a systematic method has not been established in clinical practice. Further study of the necessity for a daily melatonin profile to correctly time melatonin administration is needed. Although dosage is still an unclear issue, there is a tendency towards using much lower (approximately physiological) dosages.

Combined treatments based on chronobiology

Bright-light therapy and melatonin are known to be effective for DSPS and non-24. However, many patients do not properly respond to these treatments. Combined treatments with melatonin administration before bedtime and bright-light therapy early in the morning have been effective in some patients.[31]

Such a treatment strategy for CRSD has been proposed.[69] As a first step, it is important to reset daily-life schedules and regulate the lighting environment. Chronotherapy[70] may be useful prior to light therapy or melatonin therapy to obtain the desired sleep–wake schedule with one caveat. Although delaying both bedtime and waking time by 3 h, repeated daily until rotation around the clock can achieve the desired sleep–wake schedule, this delaying chronotherapy could lead to non-24 by allowing the system to slip around the clock and cause dangerous situations. Bright-light and/or melatonin treatment are effective for stabilizing the desired sleep–wake schedule. After the patient reaches the target bedtime, and hence rising time, there is a need for rigid adherence to the new schedule. Lighting should be dim for at least several hours before bedtime and should be as bright as possible upon wake time. The use of blue-light filtered sunglasses in the evening might be a useful strategy.[71]

Comorbidity and psychiatric symptoms

Some reports have indicated that depression is the most common psychopathology associated with DSPS.[44,72] However, the relationship between psychiatric symptoms and the biological background of CRSD has not been elucidated.

In our cohort study of 150 consecutive cases,[73] 70% were diagnosed as primary CRSD and the remaining 30% as psychiatric diseases (depression, personality disorders, anxiety disorders, or schizophrenia).

A large cohort study of 57 sighted patients with non-24[35] conducted over a 10-year period has provided important clinical information. The onset of non-24 had occurred during the teenage years in 63% of the cohort. Psychiatric disorders had preceded the onset of non-24 in 16 patients (28%); of the remaining 41 patients, 14 (34%) developed major depression after the onset of non-24.

These studies suggest that there may be a close relationship between psychiatric symptoms and CRSD. Withdrawal from a normal social life due to psychiatric problems is one of the etiologic factors of CRSD. Sighted patients with non-24 may have preceding schizophrenia, bipolar disorder, depression, obsessive–compulsive disorder or schizoid personality.[24,26,27,33] Hayakawa reported that among patients who had no psychiatric problems before the onset of non-24, 34% developed major depression thereafter. In these patients, the symptoms of depression were exacerbated when their sleep episodes occurred out of phase (i.e., when they slept during the daytime) and were slightly ameliorated when their sleep episode occurred in phase (i.e., when they slept during the night). This suggests the importance of correct phase relationships for good mood, and also that a reduction in exposure to sunlight may be a cause of depression, as described with respect to seasonal affective disorder.[74]

Some patients suffer from both depressive mood and DSPS,[73] and do not respond to antidepressants. However, intensive treatments for sleep disorders using bright light and/or melatonin are simultaneously beneficial for improving the depressive symptoms.[73] These findings indicate that CRSD and depression could share a common pathology on a chronobiological basis.

There have been various studies on the relationship between biological rhythms and depression. Some of the evidence suggests that late rising itself may predispose to depression. Wehr et al.[75] have introduced the circadian-rhythm phase-advance hypothesis, which infers that, in depression, the circadian rhythm is phase-advanced relative to the (delayed) sleep phase. Our previous studies[73,76] have revealed that the sleep phase was delayed relative to the melatonin rhythm in patients with CRSD as compared with controls. Delay of the sleep phase relative to the circadian pacemaker may be an etiologic factor of the depression associated with CRSD. Another possible trigger for this depression is the social disruption caused by CRSD.

Several disorders are also associated with DSPS, i.e., chronic or mild traumatic brain injuries[77–80] and headache.[81] Furthermore, idiopathic sleep onset insomnia in children is strongly associated with DSPS and responds very well to melatonin treatment,[82,83] as does the chronic idiopathic sleep onset insomnia in children with attention-deficit/hyperactivity disorder (ADHD).[84,85]

These recent studies have suggested an association between comorbid diseases and CRSDs, although the mechanisms underlying this association remain to be elucidated.

Biological basis and pathogenesis of CRSD

The exact mechanisms responsible for DSPS are unknown, but are surely multiple in origin. In particular, an abnormal interaction between the endogenous circadian rhythm and the sleep homeostatic process that regulates sleep and wakefulness plays an essential role in the pathophysiology of delayed sleep phase-type CRDS. Altered phase relationships relative to the light–dark cycle are a common feature in patients with delayed sleep disorders.

Voluntary wakefulness until late at night and waking up late in the morning may create an abnormal relationship between the endogenous circadian rhythm and sleep homeostasis. Several factors may contribute to the development of such disorders in these patients, for example changes in the characteristic features of the PRC, or light sensitivity, resulting in melatonin suppression.

Several biological factors possibly related to the pathogenesis of CRSD are as follows.

Sleep length

The mean habitual sleep length in patients with CRSD has been reported to be longer than that in controls; 9–10 h (9.0 ± 1.3 h; mean $\pm$ SD) in non-24.[32,35] The circadian periods of the sleep–wake cycles in patients with non-24 are between 24.5 and 25 h (24.8 ± 0.4 h; mean $\pm$ SD).

The longer sleep duration in DSPS than in healthy individuals could be socially disadvantageous because of delayed waking in the morning as well as inability to fall asleep at the desired time and staying up late at night.

Temperature rhythm and sleep phase in CRSD

Studies conducted in a time-cue-free isolation environment have demonstrated that sleep onset times cluster around the core body temperature (BT) trough.[86] The BT trough in patients with DSPS and non-24 in our study, which appeared relatively earlier in the sleep period, may indicate a common basis between what happens to humans under temporal isolation and the pathophysiology of these circadian disorders. Studies on the relationship between sleep and temperature in normal controls, and patients with DSPS and non-24 in a semi-constant routine environment have confirmed that (i) sleep length and the interval between the BT trough and sleep offset are significantly longer in non-24 patients than in DSPS patients, and that these values are significantly longer in both types of patients than in controls, and (ii) further analysis of the relative time of the BT trough in the sleep period has shown that it occurs significantly earlier in non-24 and DSPS patients than in controls.[87,88]

Deformity of the phase-advance portion

In humans, the average free-running period of the sleep–wake cycle is somewhat longer than 24 h.[84,87,88] Therefore, to be entrained to the 24-h day, the circadian pacemaker needs to be phase-advanced regularly each day. This capacity of the circadian pacemaker to phase-advance or phase-delay is well described in PRCs.[47,48] Khalsa et al. conducted an intensive study of human PRCs under highly controlled conditions and obtained a comprehensive characterization; phase delays occurred when the light stimulus was applied before the critical phase at the core body temperature minimum and phase advances occurred when the light stimulus was applied after the critical phase in a day, without a dead zone.[49] The shape of the PRC represents a subject's resetting capability. Alternatively, PRCs indicate a range of period lengths to which the circadian pacemaker can be entrained. This range is estimated to be between 23 and 26 h.[89] A more recent study indicates that the range is much smaller with a period of nearly 24 h.[90]

Czeisler et al.[70] have hypothesized that patients with DSPS may have an abnormally small advance portion of the PRC. This means that the range of period length to which the patient can be entrained is limited. This hypothesis can explain the potential resetting capacity of DSPS patients to accomplish a phase-advance equal to the difference between their endogenous free-running period and the 24-h day, as well as their lack of capacity to phase-advance their daily sleep episode to an earlier clock time.

If the PRC has an even smaller phase-advance portion, the patient fails to entrain even to the 24-h day and displays a sleep–wake cycle longer than 24 h (non-24). This might provide an explanation for a patient's failure to entrain to an environmental light–dark cycle. However, no clinical studies have confirmed these hypotheses.

Homeostatic process and circadian rhythm in CRSD

In CRSD, persistent sleep disorders are considered to be due to alterations of the circadian timekeeping system, and the basic homeostatic mechanisms seem to be normal as long as the patients are able to sleep at their desired time of day. However, some patients with CRSD complain of sleep disturbance-associated impairment of social or occupational functioning even if they are allowed to sleep. In such patients, alterations in the length of the circadian period or in the recovery of sleep function after sleep loss could be contributory factors to the development of DSPS. On the basis of this hypothesis, Uchiyama et al.[88] conducted a 24-h sleep deprivation study of patients with DSPS and non-24 under an ultra-short sleep–wake schedule. This revealed that recovery daytime sleep after 24-h sleep deprivation did not occur in these patients. The finding suggests that they may have problems related to the process of sleep homeostasis, which involves accumulating sleep pressure during sleep deprivation, and/or releasing sleep pressure after sleep deprivation. Control subjects can phase-advance sleep onset by increasing homeostatic sleep pressure, while DSPS and non-24 patients fail to advance sleep onset even after sleep deprivation.

In control subjects, after melatonin production has been initiated, sleep propensity increases in parallel with melatonin production, whereas in patients there is a lag of several hours between the onset of melatonin production and that of a major sleep episode. The lag is longer in non-24 than in DSPS. These findings indicate that there may be a phase alteration between the sleep–wake cycle and the circadian pacemaker in DSPS and non-24.

Light sensitivity to melatonin suppression

Czeisler et al.[91] have reported that some totally blind patients display suppression of melatonin secretion when their eyes are exposed to bright light. Such blind patients who displayed light-induced melatonin suppression were free from sleep disturbances, whereas most of those who did not suffered from sleep disturbances, including failure to entrain to a 24-h day. This might provide an explanation for the well-acknowledged clinical fact that some blind patients show loss of entrainment to a 24-h day (non-24), while others can maintain circadian entrainment even at a normal phase. In blind patients, as in all humans, the non-visual retinohypothalamic pathway conveying light information to the suprachiasmatic nuclei seems to play an exclusive role, and may in some patients still be functional even though their visual acuity is zero.

Patients with DSPS fail to synchronize their 24-h cycle at an appropriate phase relationship to the environment, perhaps because of reduced sensitivity to environmental cues, notably light–dark cycles.

Some sighted patients with non-24 have been reported to have decreased sensitivity to the light-induced melatonin-suppression test.[92,93] This decreased sensitivity to light may play an important role in the failure to entrain.

Aoki et al.[94,95] undertook a series of experiments to investigate the effect of light on melatonin suppression. The studies confirmed that minimum light intensity decreased as duration of exposure increased, indicating that less light intensity than previously reported could suffice for melatonin suppression, and that melatonin suppression in response to light was significantly greater in patients with DSPS than in controls, suggesting hypersensitivity to light in DSPS patients. These results are incompatible with former studies.[91–93] Hypersensitivity of melatonin suppression or of the circadian pacemaker to light may play an important role in the etiology of DSPS; evening light could easily phase-delay or free-run in DSPS or non-24 patients.

Possible hypothesis for the pathology of DSPS and non-24

The longer BT nadir-to-sleep offset interval in DSPS and non-24 compared with control subjects[87] suggests that the effectiveness of the phase-advance portion of the PRC in the morning (rising time) may be masked by the longer sleep episodes, and that consequently, the sleep phase may remain delayed in DSPS patients and show further delay in non-24 patients. This hypothesis contends that the difference between DSPS and non-24 lies in the masking of the phase-advance portion. This may also provide an explanation for the fact that a DSPS-like sleep pattern and a non-24-like sleep pattern can appear in the same patient. Evening bright-light exposure at bedtime could easily trigger phase-delay in DSPS and non-24 patients, since the phase-delay portion of the PRC in the evening (bedtime) may be exposed by the later sleep episode. Furthermore, higher sensitivity to light for melatonin suppression[95] could facilitate the delay of sleep onset even more.

Findings obtained using an ultra-short sleep–wake schedule[88] also support this hypothesis in terms of homeostatic considerations. Normal controls are expected to have two different means of phase-advancing their sleep onset time: increasing homeostatic sleep pressure by sleep deprivation, and phase-advancing the pacemaker by morning light. In contrast, patients are likely to have difficulty in elevating homeostatic sleep pressure. Thus, the only way for such patients to phase-advance sleep timing is to phase-advance the pacemaker.

Genetic factors in the etiology of DSPS and non-24

As with many other types of disease, the genetic basis for CRSD has been investigated. Patients with advanced sleep phase syndrome (ASPS) are reported to have polymorphism in the circadian clock gene.[96,97] The role of the 3111 CLOCK gene in DSPS has been supported by Iwase et al.,[98] and in the human period 3 gene, one of the haplotypes is significantly associated with DSPS.[99] So far, there have been few studies on the circadian period in DSPS and non-24 under a time-free environment, and there are no data to support the hypothesis of a longer period in DSPS and non-24 than in normal subjects. In a clinical study,[35] the period of non-24 patients was shown to be 24.3–24.8 h, which is within the normal range.

Studies of genetic factors associated with light sensitivity could provide further information on the pathogenesis of CRSD, and whether CRSD can be explained by behavioral levels of day/night exposure. Polymorphisms of the period gene may also discriminate between extreme morning and evening types.[100,101] Jones et al.[102] reported age-related changes in the association between a polymorphism in the PER3 gene, and suggested this might explain the evening-preference of younger individuals. Matsuo et al.[103] reported a novel single nucleotide polymorphism in hPer2 associated with diurnal preference in a healthy population. These lines of research could help to clarify whether DSPS is an extreme expression of "eveningness".

Accumulating studies of chronotype[8–11,13–15] have suggested similarities or differences in evening-preference individuals and DSPS patients using chronobiological markers, i.e., EEG records, body temperature and/or melatonin. Baehr et al.[13] reported that evening-type individuals slept during the earlier part of their body temperature curve, similar to DSPS patients, and Liu et al.[104] obtained supporting results in terms of melatonin peak time. Mongrain et al.[105] conducted an intensive investigation of circadian and homeostatic sleep regulation in individuals with either morningness or eveningness preference and concluded that the two regulatory mechanisms differ in the two groups. These studies may provide new insights into the biological basis of why morning-preference individuals are unsuited for night work because of their higher sleep propensity in the evening.

Future considerations

As increasing numbers of patients are presenting with CRSD, there is a need for multidirectional studies for elucidating the pathophysiology and establishing practical treatments. This review has presented several hypotheses based on our own research. Figure 1 is a schematic representation of CRSD research projects dealing with multiple factors: biological, environmental and/or psychiatric. Such research may help to raise social awareness of CRSD, and its appropriate treatment and prospective prevention in the future.

Patients with CRSD who have psychiatric, psychological or personality disorders have usually been overlooked when treatments are being considered. However, many of these patients, especially those with depression, can be improved by chronobiological treatments. This suggests a close relationship between psychiatric diseases and CRSD. Personality factors related to CRSD should also be considered when designing suitable treatments.[106,107] Increasing numbers of studies have indicated that CRSD can occur in childhood, or can be associated with ADHD, traumatic brain injury or headache. Further studies are needed to clarify the relationship between CRSD and various comorbidities. These lines of research could reveal new aspects that are relevant from the viewpoint of both psychiatry and human chronobiology.

Practice points

1. In clinical practice, a detailed psychiatric interview should be conducted to clarify any comorbidity of CRSD with psychiatric disorders.
2. Patients with psychiatric symptoms should be treated using psychiatric and chronobiological methods, and efforts should be made to find any relationship between psychiatric symptoms and CRSDs.
3. Recognition of the relatively widespread prevalence of DSPS and non-24 should be considered in the discussion of later school starting times, which ironically are most likely to affect those suffering from this type of disorder.

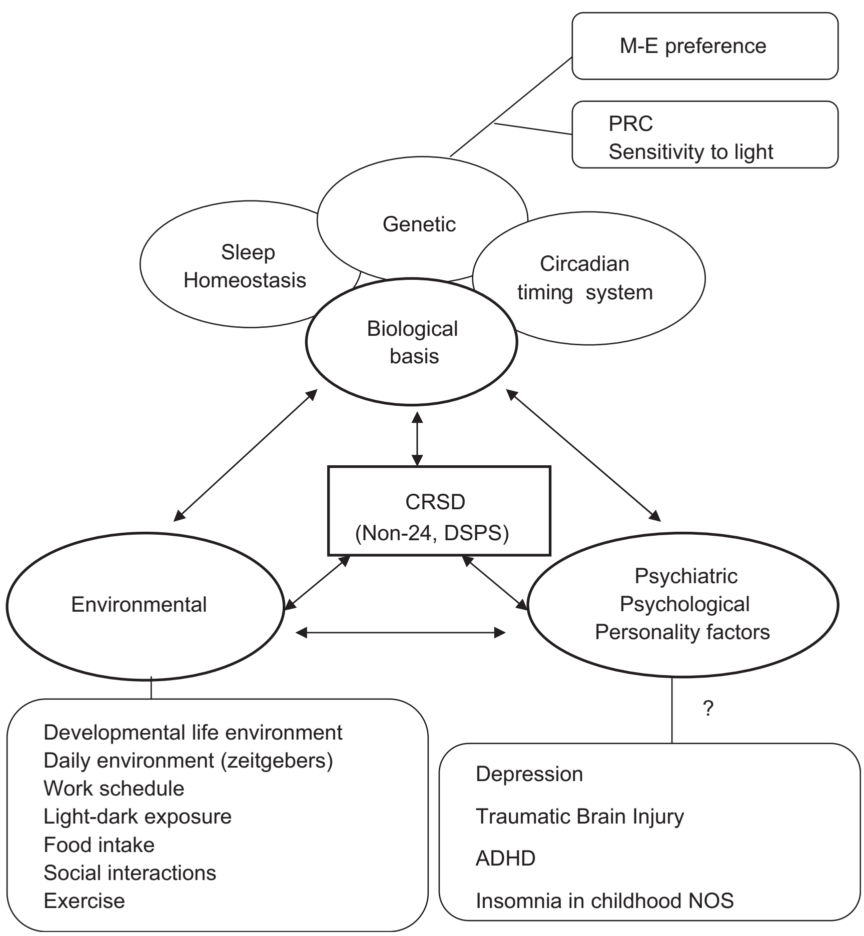

Figure 1 The future direction of CRSD research. ADHD, attention-deficit/hyperactivity disorder; CRSD, circadian rhythm sleep disorder; M-E, morningness-eveningness; NOS, not otherwise specified; PRC, phase response cure.

4. As many measured data as possible on the circadian rhythms of the sleep–wake cycle, body temperature, and/or melatonin level should be obtained in a patient suspected to suffer from CRSD to facilitate appropriate treatment with light and/or melatonin.

Research agenda

1. Cohort study of sleep hours, sleep timing, sleep disturbance and lighting conditions. This could provide information on the environmental, social, and biological basis of CRSD.
2. Obtain information on lifestyle, morningness and eveningness preference throughout development, from the neonatal period through to childhood and adolescence.
3. Future research into the roles of the circadian pacemaker and homeostatic sleep pressure in the emergence of CRSD.
4. Studies of acquisition of the PRC in patients with CRSD to elucidate the pathophysiology of CRSD and to devise practical treatment.
5. Investigation of light-induced phase shifts to test the hypothesis that patients with DSPS show hypersensitivity to night-time light exposure. According to this hypothesis, evening light exposure is particularly important in precipitating DSPS in predisposed persons.
6. The possible roles of conditioned insomnia and inadequate sleep hygiene in the exacerbation of DSPS.

References

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders: diagnostic and coding manual*, 2nd ed. IL: Westchester; 2005.
2. Weitzman ED, Czeisler CA, Coleman RM, Spielman AJ, Zimmerman JC, Dement W, et al. Delayed sleep phase syndrome. A chronobiological disorder with sleep-onset insomnia. *Arch Gen Psychiatry* 1981;**38**:737–46.
3. Ozaki N, Iwata T, Itoh A, Kogawa S, Ohta T, Okada T, et al. Body temperature monitoring in subjects with delayed sleep phase syndrome. *Neuropsychobiology* 1988;**20**: 174–7.
4. Oren DA, Turner EH, Wehr TA. Abnormal circadian rhythms of plasma melatonin and body temperature in the delayed sleep phase syndrome. *J Neurol Neurosurg Psychiatry* 1995;**58**:379.
5. Ozaki S, Uchiyama M, Shirakawa S, Okawa M. Prolonged interval from body temperature nadir to sleep offset in patients with delayed sleep phase syndrome. *Sleep* 1996; **19**:36–40.
6. Shibui K, Uchiyama M, Okawa M. Melatonin rhythms in delayed sleep phase syndrome. *J Biol Rhythms* 1999;**14**: 72–6.

*7. Roenneberg T, Wirz-Justice A, Merrow M. Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms* 2003;**18**:80–90.

8. Paine SJ, Gander PH, Travier N. The epidemiology of morningness/eveningness: influence of age, gender, ethnicity and socioeconomic factors in adults (30–49 years). *J Biol Rhythms* 2006;**21**:68–76.
9. Goulet G, Mongrain V, Desrosiers C, Paquet J, Dumont M. Daily light exposure in morning-type and evening-type individuals. *J Biol Rhythms* 2007;**22**:151–8.
10. Mongrain V, Carrier J, Dumont M. Chronotype and sex effects on sleep architecture and quantitative sleep EEG in healthy young adults. *Sleep* 2005;**28**(7):819–27.
11. Mongrain V, Lavoie S, Selmaoui B, Paquet J, Dumont M. Phase relationships between sleep–wake cycle and underlying circadian rhythms in morningness–eveningness. *J Biol Rhythms* 2004;**19**:248–57.

*12. Taillard J, Philip P, Coste O, Sagaspe P, Bioulac B. The circadian and homeostatic modulation of sleep pressure during wakefulness differs between morning and evening chronotypes. *J Sleep Res* 2003;**12**:275–82.

*13. Baehr EK, Revelle W, Eastman CI. Individual differences in the phase and amplitude of the human circadian temperature rhythm: with an emphasis on morningness–eveningness. *J Sleep Res* 2000;**9**:117–27.

14. Kerkhof GA. The 24-h variation of mood differs between morning- and evening-type individuals. *Percept Mot Skills* 1998;**86**:264–6.
15. Kerkhof GA, Van Dongen HP. Morning-type and evening-type individuals differ in the phase position of their endogenous circadian oscillator. *Neurosci Lett* 1996;**218**: 153–6.
16. Miles LE, Rynal DM, Wilson MA. Blind man living in normal society has circadian rhythms of 24.9 h. *Science* 1977;**198**: 421–3.
17. Okawa M, Nanami T, Wada S, Shimizu T, Hishikawa Y, Sasaki H, et al. Four congenitally blind children with circadian sleep–wake rhythm disorder. *Sleep* 1987;**10**:101–10.
18. Arendt H, Aldhous M, Wright J. Synchronisation of a disturbed sleep–wake cycle in a blind man by melatonin treatment. *Lancet* 1988:772–3.
19. Palm L, Blennow G, Wetterberg L. Correction of non-24 h sleep–wake cycle by melatonin in a blind retarded boy. *Ann Neurol* 1991;**29**:336–9.
20. Klein T, Martens H, Dijk DJ, Kronauer RE, Seely EW, Czeisler CA. Circadian sleep regulation in the absence of light perception: chronic non-24-h circadian rhythm sleep disorder in a blind man with a regular 24-h sleep–wake schedule. *Sleep* 1993;**16**:333–43.
21. Lapierre O, Dumont M. Melatonin treatment of a non-24 h sleep–wake cycle in a blind retarded child. *Biol Psychiatry* 1995;**38**:119–22.
22. Palm L, Blennow G, Wetterberg L. Long-term melatonin treatment in blind children and young adults with circadian sleep–wake disturbances. *Dev Med Child Neurol* 1997;**39**:319–25.

*The most important references are denoted by asterisk.

23. Kamgar-Parsi B, Wehr TA, Gillin JC. Successful treatment of human non-24-h sleep–wake syndrome. *Sleep* 1983;**6**: 257–64.
24. Sasaki T, Hashimoto O, Honda Y. A case of non-24-h sleep–wake syndrome preceded by depressive state. *Jpn J Psychiatry Neurol* 1990;**44**:191–2.
25. Oren DA, Wehr TA. Hypernyctohemeral syndrome after chronotherapy for delayed sleep phase syndrome. *N Engl J Med* 1992;**627**:1762.
26. Tagaya H, Matsuno Y, Atsumi Y. A schizophrenic with non-24-h sleep–wake syndrome. *Jpn J Psychiatry Neurol* 1993;**47**:441–2.
27. McArhur AJ, Lewy AJ, Sack RL. Non-24-h sleep–wake syndrome in a sighted man: circadian rhythm studies and efficacy of melatonin treatment. *Sleep* 1996;**19**:544–53.
28. Uchiyama M, Okawa M, Ozaki S, Shirakawa S, Takahashi K. Delayed phase jumps of sleep onset in a patient with non-24-h sleep–wake syndrome. *Sleep* 1996;**19**:637–40.
29. Nakamura K, Hashimoto S, Honma S, Honma K, Tagawa Y. A sighted man with non-24-h sleep–wake syndrome shows damped plasma melatonin rhythm. *Psychiatry Clin Neurosci* 1997;**51**:115–9.
30. Hashimoto S, Nakamura K, Honma S, Honma K. Free-running of plasma melatonin rhythm prior to full manifestation of a non-24 h sleep–wake syndrome. *Psychiatry Clin Neurosci* 1998;**52**:264–5.
31. Hayakawa T, Kamei Y, Urata J, Shibui K, Ozaki S, Uchiyama M, et al. Trials of bright light exposure and melatonin administration in a patient with non-24 h sleep–wake syndrome. *Psychiatry Clin Neurosci* 1998;**52**:261–2.
32. Watanabe T, Kajimura N, Kato M, Sekimoto M, Hori T, Takahashi K. Case of a non-24 h sleep–wake syndrome patient improved by phototherapy. *Psychiatry Clin Neurosci* 2000;**54**:369–70.
33. Morinobu S, Yamashita H, Yamawaki S, Tanaka K, Ohkawa M. Obsessive–compulsive disorder with non-24-h sleep-–wake syndrome. *J Clin Psychiatry* 2002;**63**:838–40.
34. Boivin DB, James FO, Santo JG, Caliyurt O, Chalk C. Non-24-h sleep–wake syndrome following a car accident. *Neurology* 2003;**60**:1841–3.
*35. Hayakawa T, Uchiyama M, Kamei Y, Shibui K, Tagaya H, Asada T, et al. Clinical analyses of sighted patients with non-24-h sleep–wake syndrome: a study of 57 consecutively diagnosed cases. *Sleep* 2005;**28**:945–52.
36. Yazaki M, Shirakawa S, Okawa M, Takahashi K. Demography of sleep disturbances associated with circadian rhythm disorders in Japan. *Psychiatry Clin Neurosci* 1999;**53**: 267–8.
37. Pelayo R, Thorpy M, Govinski P. Prevalence of delayed sleep phase syndrome among adolescents. *Sleep Res* 1988;**17**:392.
38. Carskadon MA, Vieira C, Acebo C. Association between puberty and delayed phase preference. *Sleep* 1993;**16**: 258–62.
39. Schuen JN, Millard SL. Evaluation and treatment of sleep disorders in adolescents. *Adolesc Med* 2000;**11**:605–16.
40. Schrader H, Bovin G, Sand T. Delayed and advanced sleep phase syndromes. *J Sleep Res* 1993;**2**:51–5.
41. Yamadera H, Takahashi K, Okawa M. A multicenter study of sleep–wake rhythm disorders: clinical features of sleep–wake rhythm disorders. *Psychiatry Clin Neurosci* 1996;**50**: 195–201.
42. Harada T, Tanoue A, Takeuchi H. Epidemiological studies on dreams, sleep habits and mental symptoms in students aged 18–25 years and the 24 h a day commercialization of Japanese society (1). *Sleep Biol Rhythms* 2006;**4**:274–81.
43. Tagaya H, Uchiyama M, Ohida T, Kamei Y, Shibui K, Ozaki A, et al. Sleep habits and factors associated with short sleep duration among Japanese high-school students: a community study. *Sleep Biol Rhythms* 2004;**2**:57–64.
44. Regestein QR, Monk TH. Delayed sleep phase syndrome: a review of its clinical aspects. *Am J Psychiatry* 1995;**152**: 602–8.
45. Dagan Y, Eisensterin M. Circadian rhythm sleep disorders: toward a more precise definition and diagnosis. *Chronobiol Int* 1999;**16**:213–22.
46. Kamei Y, Urata J, Uchiyama M, Hayakawa T, Ozaki S, Shibui K, et al. Clinical characteristics of circadian rhythm sleep disorders. *Psychiatry Clin Neurosci* 1998;**52**:234–5.
47. Honma K, Honma S. A human phase response curve for bright light pulse. *Jpn J Psychiatry Neurol* 1988;**42**:167–8.
48. Minors DS, Waterhouse JM, Wirz-Justice A. A human phase–response curve to light. *Neurosci Lett* 1991;**133**: 36–40.
*49. Khalsa SB, Jewell ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. *J Physiol* 2003;**549**:945–52.
50. Lewy AJ, Ahmed S, Jackson JM, Sack RL. Melatonin shifts human circadian rhythms according to a phase-response curve. *Chronobiol Int* 1992;**9**:380–92.
51. Alvarez B, Dahlitz MJ, Vignau J, Parkes JD. The delayed sleep phase syndrome; clinical and investigative findings in 14 subjects. *J Neurol Neurosurg Psychiatry* 1992;**55**: 665–70.
52. Arendt J, Skene DJ, Middleton B, Lockley SW, Deacon S. Efficacy of melatonin treatment in jet lag, shift work, and blindness. *J Biol Rhythms* 1997;**12**:604–17.
53. Folkard S, Arendt J, Aldhous M, Kennett H. Melatonin stabilizes sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. *Neurosci Lett* 1990;**113**:193–8.
54. Lapierre O, Dumont M, Lesperance P, Montplaisir J. Entrainment of a free running sleep–wake cycle with melatonin in a blind retarded child. *Sleep Res* 1993;**22**: 627.
55. Lapierre O, Dumont M. Melatonin treatment of a non-24-h sleep–wake cycle in a blind retarded child. *Biol Psychiatry* 1995;**38**:119–22.
56. Palm L, Blennow G, Wetterberg L. Correction of non-24-h sleep–wake cycle by melatonin in a blind retarded boy. *Ann Neurol* 1991;**29**:336–9.
57. Tzischinsky O, Pal I, Epstein R, Dagan Y, Lavie P. The importance of timing in melatonin administration in a blind man. *J Pineal Res* 1992;**12**:105–8.
58. Lockley SW, Skene DJ, James K, Arendt J. Melatonin administration can entrain the free-running circadian system of blind subjects. *J Endocrinol* 2000;**164**:R1–6.
*59. Sack RL, Brandes RW, Kendall AR. Entrainment of free-running circadian rhythms in blind people. *N Engl J Med* 2000;**343**:1070–7.
*60. Arendt J, Skene DJ. Melatonin as a chronobiotic. *Sleep Med Rev* 2005;**9**:25–39.
61. Kamei Y, Hayakawa T, Urata J, Uchiyama M, Shibui K, Kim K, et al. Melatonin treatment for circadian rhythm sleep disorders. *Psychiatry Clin Neurosci* 2000;**54**:381–2.
62. Pandi-Perumal SR, Smits M, Spence W, Srinivasan V, Cardinali DP, Lowe AD, et al. Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;**31**:1–11.
63. Arendt J. Does melatonin improve sleep? Efficacy of melatonin. *Br Med J* 2006;**332**:550.

64. Mundey K, Benloucif S, Harsanyi K, Dubocovich ML, Zee PC. Phase-dependent treatment of delayed sleep phase syndrome with melatonin. *Sleep* 2005;**28**:1271–8.
65. Van der Heijden KB, Smits MG, van Someren EJ, Boudewijn GW. Prediction of melatonin efficacy by pretreatment dim light melatonin onset in children with idiopathic chronic sleep onset insomnia. *J Sleep Res* 2005;**14**:187–94.
66. Dahlitz M, Alvarez B, Vignau J, English J, Arendt J, Parkes JD. Delayed sleep phase syndrome response to melatonin. *Lancet* 1991;**337**:1121–4.
67. Nagtegaal JE, Kerkhof GA, Smits MG, Swart AC, van der Meer YG. Delayed sleep phase syndrome: a placebo-controlled cross-over study on the effects of melatonin administered 5 h before the individual dim light melatonin onset. *J Sleep Res* 1998;**7**:135–43.
*68. Kayumov L, Brown G, Jindal R, Buttoo K, Shapiro CM. A randomized, double-blind, placebo-controlled crossover study of the effect of exogenous melatonin on delayed sleep phase syndrome. *Psychosom Med* 2001;**63**:40–8.
69. Okawa M, Uchiyama M, Ozaki S, Shibui K, Ichikawa H. Circadian rhythm sleep disorders in adolescent: clinical trials of combined treatments based on chronobiology. *Psychiatry Clin Neurosci* 1998;**52**:483–90.
70. Czeisler CA, Richardson GS, Coleman RM, Zimmerman JC, Moore-Ede MC, Dement WC, et al. Chronotherapy: resettinng the circadian clocks of patients with delayed sleep phase insomnia. *Sleep* 1981;**4**:1–21.
71. Sasseville A, Paquet N, Sévigny J, Hébert M. Blue blocker glasses impede the capacity of bright light to suppress melatonin production. *J Pineal Res* 2006;**41**: 73–8.
72. Thorpy MJ, Korman E, Spielman AJ, Glovinsky PB, et al. Delayed sleep phase syndrome in adolescents. *J Adolesc Health Care* 1988;**9**:22–7.
73. Uchiyama M. Circadian rhythm sleep disorders and depression. *Jpn J Clin Psychopharm* 2004;**7**:1037–47.
74. Wehr TA, Jacobsen FM, Sack DA, Arendt J, Tamarkin L, Rosenthal NE. Phototherapy of seasonal affective disorder. Time of day and suppression of melatonin are not critical for antidepressant effects. *Arch Gen Psychiatry* 1986;**43**: 870–5.
75. Wehr TA, Wirz-Justice A, Goodwin FK, Duncan W, Gillin JC, et al. Phase advance of the circadian sleep–wake cycle as an antidepressant. *Science* 1979;**206**:710–3.
76. Uchiyama M, Shibui K, Hayakawa T, Kamei Y, Ebisawa T, Tagaya H, et al. Larger phase angle between sleep propensity and melatonin rhythms in sighted humans with non-24-h sleep–wake syndrome. *Sleep* 2002;**25**:83–8.
77. Ayalon L, Borodkin K, Dishon L, Kanety H, Dagan Y. Circadian rhythm sleep disorders following mild traumatic brain injury. *Neurology* 2007;**68**:1136–40.
78. Nagtegaal JE, Kerkhof GA, Smits MG, Swart AC, van der Meer YG. Traumatic brain injury-associated delayed sleep phase syndrome. *Funct Neurol* 1997;**12**:345–8.
79. Smits MG, Nagtegaal JE. Post-traumatic delayed sleep phase syndrome. *Neurology* 2000;**55**:902–3.
80. Wieringen SV, Jansen T, Smits MG, Nagtegaal JE, Coenen AML. Melatonin for chronic whiplash syndrome with delayed melatonin onset. Randomised, placebo-controlled trial. *Clin Drug Invest* 2001;**21**:813–20.
81. Nagtegaal JE, Smits MG, Swart AC, Kerkhof GA, van der Meer YG. Melatonin-responsive headache in delayed sleep phase syndrome: preliminary observations. *Headache* 1998;**38**:303–7.
82. Smits MG, Nagtegaal JE, van der Heijden J, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. *J Child Neurol* 2001;**16**:86–92.
83. Smits MG, van Stel HF, van der HK, Meijer AM, Coenen AM, Kerkhof GA. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2003;**42**:1286–93.
84. Van der Heijden KB, Smits MG, Gunning WB. Idiopathic chronic sleep onset insomnia in Attention-Deficit/Hyperactivity Disorder: a circadian rhythm sleep disorder. *Sleep Med* 2005;**6**(Suppl. 2):s178.
85. Van der Heijden KB, Smits MG, van Someren EJ, Ridderinkhof KR, Gunning WB. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adolesc Psychiatry* 2007;**46**: 233–41.
86. Czeisler CA, Weitzman ED, Moore-Ede MC, Zimmerman JC, Knauer RE. Human sleep: its duration and organization depend on its circadian phase. *Science* 1980;**210**:1264–7.
*87. Uchiyama M, Okawa M, Shibui K, Kim K, Tagaya H, Kudo Y, et al. Altered phase relation between sleep timing and core body temperature rhythm in delayed sleep phase syndrome and non-24-h sleep–wake syndrome in humans. *Neurosci Lett* 2000;**294**:101–4.
*88. Uchiyama M, Okawa M, Shibui K, Liu X, Hayakawa T, Kamei Y, et al. Poor compensatory function for sleep loss as a pathologic factor in patients with delayed sleep phase syndrome. *Sleep* 2000;**23**:553–8.
89. Weber AL, Cary MS, Connor N, Keyes P. Human non-24-h sleep–wake cycles in an everyday environment. *Sleep* 1980;**2**:347–54.
90. Wright KP, Hughes RJ, Kronauer RE, Dijk DJ, Czeisler CA. Intrinsic near-24-h pacemaker period determines limits of circadian entrainment to a weak synchronizer in humans. *Proc Natl Acad Sci USA* 2001;**98**:14027–32.
91. Czeisler CA, Shanahan TL, Klerman EB, Martens H, Brotman DJ, Emens JS, et al. Suppression of melatonin secretion in some blind patients by exposure to bright light. *N Engl J Med* 1995;**332**:6–11.
92. Hashimoto S, Nakamura K, Honma S, Honma K. Free-running circadian rhythm of melatonin in sighted man despite a 24-h sleep pattern: a non-24-h circadian syndrome. *Psychiatry Clin Neurosci* 1997;**51**: 109–14.
93. McArthur AJ, Lewy AJ, Sack RL. Non-24-h sleep–wake syndrome in a sighted man: circadian rhythm studies and efficacy of melatonin treatment. *Sleep* 1996;**19**:544–53.
94. Aoki H, Yamada N, Ozeki Y, Yamane H, Kato N. Minimum light intensity required to suppress nocturnal melatonin concentration in human saliva. *Neurosci Lett* 1998;**252**: 91–4.
95. Aoki H, Ozeki Y, Yamada N. Hypersensitivity of melatonin suppression in response to light in patients with delayed sleep phase syndrome. *Chronobiol Int* 2001;**18**:263–71.
96. Jones CR, Campbell SS, Zone SE, Cooper F, DeSano A, Murphy PJ, et al. Familial advanced sleep-phase syndrome: a short-period circadian rhythm variant in humans. *Nat Med* 1999;**5**:1062–5.
97. Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, et al. An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science* 2001;**291**: 1040–3.
98. Iwase T, Kajimura N, Uchiyama M, Ebisawa T, Yoshimura K, Kamei Y, et al. Mutation screening of the human Clock gene in circadian rhythm sleep disorders. *Psychiatry Res* 2002;**109**:121–8.

99. Ebisawa T, Uchiyama M, Kajimura N, Mishima K, Kamei Y, Katoh M, et al. Association of structural polymorphisms in the human period3 gene with delayed sleep phase syndrome. *EMBO Rep* 2001;**2**: 342–6.
100. Archer SN, Robilliard DL, Skene DJ, Smits M, Williams A, Arendt J, et al. A length polymorphism in the circadian clock gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep* 2003;**26**: 413–5.
101. Pereira DS, Tufik S, Louzada FM, Benidito-Siliva AA, Lopez AR, Lemos NA, et al. Association of the length polymorphism in the human PER3 gene with the delayed sleep-phase syndrome: does latitude have influence upon it? *Sleep* 2005;**28**:29–32.
102. Jones KHS, Ellis J, von Schantz M, Skene DJ, Dijk D-J, Archer S. Age-related changes in the association between a polymorphism in the PER3 gene and preferred sleep and waking activities. *J Sleep Res* 2007;**16**:12–6.
103. Matsuo M, Shiino Y, Yamada N, Ozeki Y, Okawa M. A novel SNP in hPer2 associates with diurnal preference in a healthy population. *Sleep Biol Rhythms* 2007;**5**:141–5.
104. Liu X, Uchiyama M, Shibui K, Kim K, Kudo Y, Tagaya H, et al. Diurnal preference, sleep habits, circadian sleep propensity and melatonin rhythm in healthy human subjects. *Neurosci Lett* 2000;**280**:199–202.
105. Mongrain V, Carrier J, Dumont M. Circadian and homeostatic sleep regulation in morningness–eveningness. *J Sleep Res* 2006;**15**:162–6.
106. Shirayama M, Shirayama Y, Iida H, Kato M, Kajimura N, Watanabe T, et al. The psychological aspects of patients with delayed sleep phase syndrome (DSPS). *Sleep Med* 2003;**4**:427–33.
107. Iwamitsu Y, Ozeki Y, Konishi M, Murakami J, Kimura S, Okawa M. Psychological characteristics and the efficacy of hospitalization treatment on delayed sleep phase syndrome patients with school refusal. *Sleep Biol Rhythms* 2007;**5**:15–22.