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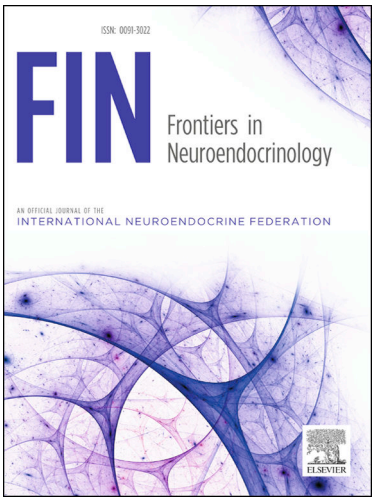

Timing is everything: circadian rhythms and their role in the control of sleep

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Revision 3

Timing is everything: circadian rhythms and their role in the control of sleep

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Abstract

Sleep and the circadian clock are intertwined and have persisted throughout history. The suprachiasmatic nucleus (SCN) orchestrates sleep by controlling circadian (Process C) and homeostatic (Process S) activities. As a "hand" on the endogenous circadian clock, melatonin is critical for sleep regulation. Light serves as a cue for sleep/wake control by activating retino-recipient cells in the SCN and subsequently suppressing melatonin. Clock genes are the molecular timekeepers that keep the 24 h cycle in place. Two main sleep and behavioural disorder diagnostic manuals have now officially recognised the importance of these processes for human health and well-being. The body's ability to respond to daily demands with the least amount of effort is maximised by carefully timing and integrating all components of sleep and waking. In the brain, the organization of timing is essential for optimal brain physiology.

Key words:

Circadian clock, Clock genes, Sleep, Sleep medicine, Sleep disorder

Introduction

The earth's daily rotational cycle has a pervasive influence on all living beings. It has guided biological events and all related processes of adaptation. Historically, the interactions of this daily cycle with organismal physiology has always been assumed but was not investigated scientifically until modern times. In the 1960s, Aschoff and his colleagues carried out a pioneering study of how humans respond to living in an underground bunker, i.e., artificially isolated from exposure to the earth's repetitive day and night cycles. The investigators found that, despite being restricted from experiencing normal environmental influences, the subjects' bodily rhythms of temperature variation and maintenance, urine excretion, and other behavioral activities persisted with a near 24 h periodicity. The finding that this periodicity diverged only slightly from the 24 h pattern observed in humans living under the influence of a regular light/dark (LD) cycle provided proof for the existence of an endogenous clock system (Aschoff, 1965). The term circadian (daily; L. *Circa*=about; *dies*=day; ~24h cycles) rhythm refers to any biological process which exhibits such an endogenous, entrainable oscillation of an approximately, but not exactly, 24 h period (Halberg et al., 1959). This endogenous circadian clock is remarkably widespread in all living organisms, from prokaryotes (e.g. cyanobacteria) to

eukaryotes (e.g. higher plants and animals). These circadian timing processes both regulate and coordinate a wide variety of rhythmic outputs which occur at molecular, physiological, and behavioral levels. These include processes involved in gene expression, regulation of the sleep/wake cycle, hormonal and metabolic regulation, thermoregulation, and a number of others (Cox and Takahashi, 2020; Kim and Lazer, 2020; Riji-Ferreira and Takahashi, 2019; Li et al., 2013; Sukumaran et al., 2010; Waterhouse et al., 2005; Richter, 1967, 1960).

The current review, on the other hand, will seek to provide a broad overview of the relationship between the circadian clock and sleep, which, according to some evaluations, continues to merit closer attention (Borbély et al., 2016; Dijk and Lockley, 2002; Foster, 2020). Some of the more recent findings of the implications of this relationship for physical and mental health will also be reviewed. In the presence of ambient time cues, circadian rhythms can be synchronised; yet, they can also persist even without them (Eban-Rothschild and Bloch, 2012; Honma et al., 2003; Mistlberger and Skene, 2004). The environmental LD cycle acts as the prominent *zeitgeber* (time giver) that resets the circadian clock daily to remain in synchrony with external time cues. However, the persistence of such near 24 h rhythms under prolonged periods of constant

environmental conditions demonstrates the existence of the endogenous circadian clock (Aschoff, 1965). This endogenously generated rhythm is sensitive to and can be changed by environmental geophysical information. This responsiveness helps to maintain a stable phase relationship between the organism and its environment, thereby adjusting those physiological variables as needed for survival (Pontes et al., 2010).

In humans, as in other mammals, these circadian processes are closely affected by a tiny group of melanopsin-expressing retinal ganglion cells (mRGCs) that are highly photosensitive to blue light. Among their other functions, these cells contribute to the mediation of circadian entrainment (Dacey et al., 2005; Esquiva et al., 2017; Hannibal et al., 2017; Nasir-Ahmad et al., 2019; Stachurska and Sarna, 2019; Zele et al., 2011). The retinohypothalamic tract (RHT) is sufficient to maintain the entrainment of circadian clock function (Dai et al., 1998; Klein and Moore, 1979; Sadun et al., 1984). Circadian self-sustaining oscillators are also found in most cells and are made up of a cell-autonomous transcriptional-translational feedback loop system that is decentralized throughout the body. It is, however, the basal hypothalamic suprachiasmatic nucleus (SCN), which is the master circadian clock in mammals, and it is their constituent nuclei which, on a daily basis, orchestrate the

overt rhythms which occur throughout the organism (Dai et al., 1998; Inouye and Kawamura, 1979; Moore and Lenn, 1972; Ralph et al., 1990; Stephan and Zucker, 1972). As a diurnal species, humans normally sleep at night (Lavie, 2001; Webb, 1994). However, there is considerable flexibility in sleep timing in a given individual. This flexibility, in turn, is determined by several factors and ultimately makes up what has been termed a two-process model. Herein, we discuss the current knowledge of sleep-wake timing, its known regulatory disorders, and its multiple implications for brain dysfunction.

Clock genes

At the molecular level, clock genes and their proteins control the rhythmic oscillations for 24 h periodicity. Initially, the transcription factors CLOCK and BMAL1 are encoded from *Clock* and *Bmal1*. These in turn produce heterodimers that permit the transcription of *Per* genes (*Per1*, *Per2* & *Per*3) and two *Cry1 & Cry2* genes in mammals. Molecular complexes are then formed from the dimerization of PER and CRY proteins. These are then transferred into the nucleus from which they originated and then proceed to prevent the expression of their proteins. Additionally, REV-ERBα and RORα interact with BMAL1 to repress and activate transcription, respectively. While it has not been consistently observed in the SCN, NPAS2 alternatively functions

as a dimerization partner for BMAL1 and can similarly regulate circadian processes in the forebrain. In addition, the products of clock genes i.e., their proteins are phosphorylated by *CKIε &CKIδ*, as well as *glycogen synthase kinase3,* a homologue of *Drosophila shaggy.* Also, they are degraded by agents such as FBXL3 and β-TRCPl, which are components of ubiquitin ligase complexes. These work cooperatively to control the circadian oscillatory period by controlling the levels and transport of PER and CRY (Hastings et al., 2018; Wulff et al., 2010). Changes have been noted in the expression of clock genes of shift workers when compared to those who work normal shifts (Bracci et al., 2014; Taniyama et al., 2015). Moreover, subjects in sleep deprivation studies show similar alterations in clock genes, findings that underscore the importance of clock genes and sleep interactions (Franken and Dijk, 2009). The regulation of clock genes is associated with the usual steps involved in gene expression regulation, including, e.g., modifications in post-transcriptional and post-translational processes (Mure et al., 2018; Takahashi, 2017). A few significant proportions of the genome and transcriptome are expressed in a circadian oscillation. A new study on a primate diurnal transcriptome atlas, which contained a wide variety of major neural and peripheral tissues, found that 82 percent of genes were rhythmic in at least one region of the tissue (Mermet et al., 2017).

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The circadian timing system interacts with the sleep/wake homeostatic process. Sleep advances or delays occur when lighting exposure is similarly advanced or delayed. The level of SCN electrical activity follows a normal pattern, with greater activity occurring in the daytime hours when compared to the biological night. Aside from the circadian regulation of firing rate, neurons in the SCN fire at higher rates during REM sleep and lower rates during NREM sleep (Deboer et al., 2003). It's been postulated that modifying the SCN neurons' firing rate during sleep can potentially alter the molecular feedback loops that are essential for sustaining the circadian timing system (Colwell and Michel, 2003). Inasmuch as there is close integration between the sleep homeostat and the circadian oscillator, the amount of slow wave and REM sleep that has taken place in the preceding sleep/wake cycle can be monitored by the circadian system. Furthermore, in mice, the SCN consolidates the sleep/wake cycle by generating an arousal signal during the subjective night (i.e., the active period), allowing it to change baseline sleep quantity (Easton et al., 2004). Although the SCN is not directly involved in sleep homeostasis, as demonstrated by an increase in electroencephalographic delta power following sleep deprivation, it does play a critical function in sleep regulatory control that extends beyond the timing of the states of vigilance.

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Mutation of clock genes affects the homeostatic process which results in the alteration of sleep architecture and duration (Archer et al., 2018; Maire et al., 2014). Altered single nucleotide polymorphisms have been reported in four major clock genes (*Clock, Per, Cry, and Bmal1*), and have been found in autism spectrum disorder (ASD) (Nicholas et al. 2007; Yang et al. 2016), depression-related disorders (Serretti et al. 2005; Shi et al. 2016), and bipolar disorder (Benedetti et al. 2003; Karthikeyan et al. 2014). Similar dysfunctionalities in clock genes have been noted in attention deficit hyperactivity disorder (ADHD) (*Clock*) (Kissling et al. 2008; Xu et al. 2010), and schizophrenia (Takao et al. 2007; Zhang et al. 2011) (*Clock*). Other work has shown that, in addition to the genes noted above, clock gene involvement occurs in psychiatric disorders such as winter depression, ASD, and schizophrenia (*Npas2*), bipolar disorder (*RORα* and *RORβ*), and ASD (*Timeless*, *DBP*, and *CK1ε*) (Charrier et al., 2017). The overlap of identical clock gene occurrence in different psychiatric disorders implies that common pathways and etiopathology may underlie these disorders. Evidence indicates that the clock genes *Cry1, Cry2, Per2,* and *Npas2* are likely to have an association with major depressive disorder (MDD), while the gene *Timeless* is a promising candidate for association with sleep disorder in MDD (Melhuish Beaupre et al., 2018).

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Studies have noted that the activity of the circadian timing system is affected significantly by the sex of the individuals. Certain disparities between men and women exist in the architecture, physiology, and pathology of the circadian endocrine rhythms (reviewed elsewhere, Nicolaides and Chrousos, 2019). Between males and females, differential regulation of daily rhythm of clock gene expression has also been seen at the molecular level; additional parameters include, but are not limited to, timing, duration, and phase of melatonin and body temperature rhythms, morningness-eveningness, and the entrained phase (Lim et al., 2013; Duffy et al., 2011). The SCN and its afferent and efferent circuits, and peripheral rhythms vary according to the sex of the individuals. The molecular dialogue between the circadian timing system and the hypothalamic-pituitary-adrenal (HPA) axis, as well as other behavioural rhythms, differs between men and women (Nicolaides and Chrousos, 2019). Factors that might affect the interpretation of these findings include uncontrolled experimental conditions, masking effects from environmental and behavioral factors, along with variation in timing and phase. Substantial circadian misalignment, as found in shift work, jet lag, sleep deprivation, or clock gene knockout animals, has been linked to major impairments in reproductive function. Alterations in hormone secretion patterns, reduced conception rates, greater

miscarriage rates, and an increased risk of breast cancer are just a few of these inadequacies. Because disrupted hormone cycles might further affect clock gene expression patterns, female health may be especially vulnerable to the impacts of desynchronizing work hours. Estrogen, for example, affects the expression of clock genes in the uterus, ovaries, and SCN (Mahoney, 2010).

Two-process model of sleep regulation

The two-process model of sleep regulation, proposed by Borbély and others, is based on the notion that the circadian clock and sleep are linked. (Borbély, 1982). The model includes a sleep-independent circadian mechanism (Process C) as well as a sleep-dependent homeostatic process (Process S) that regulates waking and sleeping times. The circadian component of sleep is closely related to circadian rhythms of metabolic and endocrine events and has an adaptive significance. In contrast, the impact of Process S is derived from sleep debt (i.e. build-up of homeostatic sleep drive or sleep pressure) accumulated during waking followed by an exponential decline during sleep. The level of Process S at sleep onset is responsible for the increase in sleep tendency, and is, therefore, heavily influenced by prior wakefulness. Process C is dictated by the recurrent variations in sleep tendency (SP) i.e. the ability to fall asleep) and thus presumably is controlled by a circadian

pacemaker. This model, therefore, accounts for how the combined action of the two processes is responsible for the onset and the duration of sleep.

This model was subsequently elaborated into a quantitative version of a model that included the ultradian (a period shorter than 24 h) dynamics of sleep as related to the NREM/REM sleep cycle (Borbély and Achermann, 1999). It was further noted that the time course of EEG slow-wave activity (SWA), which is a tightly regulated process, is the major marker of NREM sleep homeostasis. Individual differences in Process S were found, and particularly in its build-up and dissipation were found (Rusterholz et al., 2010). Subsequently, the same group observed that the time constants for dissipation seemed to follow two independent traits (Rusterholz et al., 2017). A modification of the two-process model proposed that Process S might increase during sleep and diminish during wakefulness (Putilov et al., 1999). Furthermore, circadian modulation affects displaced sleep processes (time constants and asymptotes), sleep deprivation, and homeostatic baseline sleep. The two-process model was subsequently developed to show that the reaction to sleep deprivation in both long and short sleepers could be predicted by using the same S time constants (Aeschbach et al., 2017). More S is found in short-sleepers than long-sleepers. It has

been found that, when compared to the S of long sleepers, higher levels occur in short sleepers. Nakao and coworkers developed a model of thermoregulatory feedback control modulated by two circadian oscillators, one a temperature rhythm, the other mediating sleepiness. The homeostatic pattern, sleep timing, and sleep deprivation aspects of sleep cycles were developed by integrating heat load during awake and heat loss during sleep (Nakao et al., 1995a, Nakao et al., 1995b).Kronauer conceived a model of how light affects human circadian rhythms. This model accounts for the influence of light pulses and their intensity on the pacemaker phase and amplitude. Additionally, it describes their entrainment effects (Klerman et al., 1996; Kronauer, 1990).The two-process model with homeostatic S and C processes was shown to be considerably comparable to a model based on mutual inhibition of sleep-promoting neurons in the ascending arousal system (Skeldon et al., 2014). This reciprocal inhibition model is commonly used as a tool for understanding a wide range of sleep-wake events, as well as for practical applications including the design of shift work schedules that are minimally disruptive to endogenous cycles. .

A study of the two-process model can thus provide insights into the functioning of mutual inhibition between the respective processes. Borbély recently modified the original two-process model. The SCN is now thought to orchestrate and integrate

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rhythms rather than simply generate and drive them, and interactions between processes are now regarded as continuous (Borbély et al., 2016). Homeostasis of (as-yet-undefined components of) brain function, according to the model, can be achieved through the periodic transitions occurring between sleep and wakefulness, which themselves are produced by either an internal oscillator that is separate from the SCN or due to oscillations resulting from behavioral relaxation within Process S (Borbély et al., 2016). Definitive conclusions about this issue require additional research. An alternative hypothesis has suggested that a relaxation-type sleep-wake switch exists which is based on both orexinergic (wakefulness) and homeostatic (sleepiness) drives (Fulcher et al., 2014; Phillips et al., 2011). One of these models (Fulcher et al., 2014) proposes a combined action process, i.e., that wake-active processes are due to actions of monoaminergic neurons (in the brainstem and hypothalamus) that are mutually inhibitory, and that these processes operate in parallel with ventrolateral preoptic (VLPO) neurons in the hypothalamus.

According to this concept, orexinergic neurons stabilize prolonged waking episodes via excitatory input to monoaminergic neurons in the brainstem. The VLPO neurons inhibit both orexinergic and monoaminergic neurons during sleep, and the resulting diminution in orexinergic input indirectly promotes

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sustained sleep. The model predicts that differences in orexin levels cause a change in sleep timing, with delays in the normal sleep episode being correlated with higher orexin levels (Fulcher et al., 2014). The orexinergic promotion of wakefulness is fully compatible with the two-process model because it is controlled by circadian processes and parallels the daily increase in Process C. These processes further support a model of cooperativity between sleep homeostatic mechanisms and the circadian clock.

Experiments carried out with clock gene mutant mice have revealed that clock genes may also be involved in sleep homeostasis, including changes in sleep length and depth. (see for example Kinoshita et al., 2020; Zaki et al., 2020). EEG investigations of slow wave activity (SWA) at various circadian phases, as well as additional modelling of sleep homeostatic processes, especially those happening outside of the regular circadian sleep phase, all support the conclusion that the circadian clock has a broad impact on sleep homeostasis These effects could be attributed to the clock's influence on the duration and the quality of the sleep/wake process (Deboer, 2018; Lazar et al., 2015; Münch et al., 2010).

Neural basis of the sleep-wake cycle (Process S)

The neural model of sleep-wake regulation in common use until recently evolved from the initial findings of von Economo in patients with viral disease-causing encephalitis lethargica (Von Economo, 1930). This work suggested that the brainstem had wake-promoting effects on the forebrain while sleep promotion from the anterior hypothalamus opposed this waking effect. Subsequent refinement of this hypothesis proposed the existence of wake-promoting and sleep-promoting cell groups (Saper et al., 2005). In this revision cholinergic neurons in the pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei of the upper brainstem, the serotonergic dorsal raphe nuclei (DRN), and noradrenergic locus coeruleus (LC) were thought to be responsible for wake promotion (Aston-Jones and Bloom, 1981; Jouvet, 1972). Sleep promotion was provided by GABAergic innervation from the median preoptic nuclei and ventrolateral preoptic nuclei to wake-promoting regions (Sherin et al., 1998; Suntsova et al., 2002; Suntsova and Dergacheva, 2003).

With the advent of new technologies, such as optogenetics, and CRISPR-Cas, there have been major advances in the understanding of this neuronal circuitry (Shiromani and Peever, 2017). The sleep-wake alterations in melanin-concentrating hormone (MCH) and hypocretin/ orexin (OX) activity, proposed earlier by Saper et al. (2005), have now been validated in

several studies (Fuller et al., 2006; Hassani et al., 2011; Jones and Hassani, 2013). In humans, for example, it has been found that OX levels in amygdala dialysates are higher during wake onset, while MCH levels are higher at sleep onset (Blouin et al., 2013). Also shown were correlations with emotional states. This work has supported the conclusion that activation of OX and MCH neurons in the lateral hypothalamus are respectively involved in regulating waking and REM sleep (Yamashita and Yamanaka, 2017). Moreover, fast glutamate and GABA neurotransmission have recently been proposed to be the backbone of the wake-sleep regulatory system, while the monoamine and cholinergic systems are relegated to a modulatory role (Jones, 2019; Saper and Fuller, 2017). In these fast neurotransmitter systems, there are vesicular transporters for GABA and for glutamate which are essential for synaptic neurotransmission (Tong et al., 2008, 2007). The processes of wake and sleep promotion are mutually inhibitory and therefore form the process S part of the Borbély theory (Boes et al., 2018). During waking the need for sleep gradually increases (a homeostatic process) and when sleep promotion outweighs wake promotion there is a rapid switch into sleep, which has been described as akin to an electric "flip-flop" switch (Saper, 2013). However, a higher degree of regulation is involved in the timing of this process. This occurs in the lateral hypothalamic

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area outside of the SCN where it is influenced by neuronal input from the circadian system (Process C) inside the SCN. In addition, brain's adenosine system affects arousal and thus gating of slow wave sleep (SWS) expression is influenced by adenosine levels. This in turn can prolong or shorten the duration of the basic functions of sleep and its homeostasis (Lazarus et al., 2019).

Circadian rhythm regulation (Process C)

As previously stated, light is the most powerful synchronizer of the human circadian timing system. The following factors and/or consequences have been identified as key influencers of circadian responses: 1., the organism's circadian phase when exposure to light occurs; 2., properties of the light stimulus or organism-light interaction, such as wavelength, length of the exposure time, and intensity; and 3., the effect of artificial lighting or sunlight on circadian rhythm timing. (Gooley, 2017). Secondary, non-photic factors in regulating circadian rhythms are food intake (Frank et al., 2021) and physical exercise (de Souza Teixeira et al., 2020). Other *zeitgeber* effects have been reported but full documentation of these effects is still ongoing (Atkinson et al., 2007; Cardinali et al., 2002; Youngstedt et al., 2019). The circadian timing system is more responsive to light during the

biological night, i.e., during normal sleeping hours. As a consequence, atypical sleeping schedules, such as delayed bedtime or early morning awakening, might result in a resetting of circadian clock when combined with nocturnal light exposure. This in turn will express as changes in SCN activity, as well as parallel changes in melatonin secretion. If an individual is exposed to light in the early part of the biological night, a phase delay in the circadian system may occur, i.e., melatonin secretion onset may take place later in the day after light exposure. This effect is similar to that experienced by transmeridian jet passengers when traveling westward (Czeisler et al., 1989). By contrast, individuals exposed to light late at night or in the early morning hours may experience a circadian phase advance.

The intensity of a light stimulus closely affects its circadian resetting potency. This effect is not linear however since the resetting effects occurring in the early part of continuous light exposure are stronger than those occurring later. This has led to the suggestion that a series of shorter light pulses could be more effective in resetting circadian rhythms than a single long exposure to continuous light (Najjar and Zeitzer, 2016). Amplitude differences in circadian responses to longer versus shorter wavelengths of light, as well as their

integration times, enable us to easily assess the relative contributions of melanopsin and cone photoreceptors to circadian photoreception (long for melanopsin, short for other opsins) (Van Der Meijden et al., 2016). In addition to the SCN, the RHT projects melanopsin-containing fibres to various parts of the brain, including those regions that are associated with the circadian and sleep/wake control, photic, and non-photic SCN regulation, and pupillary responses (Gooley et al., 2003; Morin, 2013) The extent to which these inputs may influence color vision is still under investigation (Stachurska and Sarna, 2019).

Until the beginning of the industrial revolution, humans lived in a mostly stable light exposure system, i.e., one that was characterized by predictable daily or seasonal oscillations in the occurrence of sunlight. Before the widespread adoption of artificial lighting, any oscillatory disruptions to the circadian systems of most living beings, particularly humans, were fairly uncommon. By contrast, people living in today's 24 h society are subject to various types of artificial illumination on a regular and continuing basis. These sources include, but are not limited to, ceiling lights, street lamps, television units, computers, and more recently, excessive use of tablets and smartphones. Many experimental studies have been conducted

to characterize the phase resetting effects of illumination, but few studies have been carried out on the adverse circadian effects of artificial lighting under conditions that prevail in the real world (Emens, 2017; Stothard et al., 2017). Artificial light created by electrical devices interacts with the human circadian system and this affects the health of individuals (Münch et al. 2020). The daily cycle of sleep and awakening is maintained by a combination of natural/artificial light during the day and darkness at night. An individual's history of light exposure, including its timing and duration, as well as other factors, such as its quantity, intensity, spatial distribution, and spectral power, are all important variables that affect the human circadian timing system (Chang et al. 2011 & Figueiro, 2013). When the internal time keeping system was exposed to artificial light in the evening , a phase delay occurred, whereas exposure to bright light triggered an advance in the circadian phase. Natural sunlight has a potential range of intensity of around 100,000 lx, this may be reduced to 25,000 lx in closed environments, while artificial lighting, such as that which occurs in offices, is around 400-500 lx (Blume et al., 2019). However, the human circadian system has a non-linear response to light, i.e., relatively low light levels can generate a relatively large response. It was also found in a small group of study that light intensities as low as 100 lx

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were sufficient to entrain the human circadian system. The same study also found that entrainment occurred in one individual in response to a light intensity of only 25 lx (Gronfier et al. 2007). Confirmatory evidence has been provided by several dose-response studies showing that low light levels can be highly impactful for the circadian system, even those well below 100 lx (Boivin et al. 1996; Zeitzer et al. 2000; Phillips et al. 2019). In addition, a half-maximum response for phase shifting required only 80-160 lx (Zeitzer et al. 2000) while only 30 lx was needed to suppress evening melatonin levels by 50% (Phillips et al. (2019).

In today's 24/7 society, night time exposure to a significant amount of artificial lighting is a pervasive and prominent phenomenon. It has been found that individuals who have only a reduced amount of natural sunlight exposure but who are also exposed to nocturnal electric lighting tend to exhibit a delayed onset of melatonin release. This finding of a late onset of subjective biological light has been associated with further disruptions in the in sleep/wake timing in such individuals (Wright et al. 2013). Light emitting devices appear to produce similar effects. One study found that individuals who read an electronic book (with a light emitting luminence of 30-32 lx) for 3-4 h prior to the bedtime exhibited delayed sleep

onset, decreased melatonin synthesis, and delayed timing of the circadian clock when compared to those who read with printed paper books (Chang et al. 2015). Further, it was found that individuals who were exposed in the evening to a range of light intensities (30-50 lx for 5 h) showed variations in melatonin suppression (Phillips et al. 2019) indicating the interindividual differences exist in how the human circadian timing system responds to day light and evening light exposure.

The negative impact caused by the exposure to light in the evening is significant. The effects of light-induced circadian disruption, which is directly the result of melatonin suppression and reduced melatonin synthesis, has further consequences which may result in sleep disruption, as well as impairments to thermoregulation, blood pressure responses, and glucose homeostasis (Gooley et al., 2011). It has thus been argued that night time exposure to artificial light, which differs in its spectral composition and intensity from natural sunlight, could be considered a potential physiological stressor (Grubisic et al., 2019).

Interactions between Process S and Process C

The circadian timing system and the sleep/wake cycle communicate in a variety of ways, most importantly in the timing of sleep onset (see Fig 1). However, the detailed neurobiology of these

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interactions still needs to be elucidated. Defining the neural pathways, neurotransmitters, and neuromodulators that participate in these interactions will potentially lead to the development of novel treatment modalities for several circadian rhythm sleep dysfunctions.

<<<<< Insert Figure 1 about here>>>>>

Melatonin and circadian rhythms

Melatonin is synthesized in the pineal gland and secreted into the cerebrospinal fluid (CSF) of the posterior third ventricle and the blood. This activity occurs exclusively at night (Pandi-Perumal et al., 2006; Reiter et al., 2014). Melatonin levels in both the CSF and plasma remain low during the day but become elevated at night, all in accordance with a circadian rhythm that is under control of the master oscillator, the SCN; this cadence however is more apparent in the CSF, where its amplitude is greater than it is in the blood. The final control over melatonin's circadian rhythm is due to postganglionic sympathetic signaling, which itself is affected by inputs from several sources; in addition to the SCN, these include the hypothalamic paraventricular nucleus (PVN), polysynaptic projections to the intermediolateral column of the cervical spinal cord, and preganglionic (PG) projections to the superior cervical ganglion (SCG) (see Fig 2). The dim light

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melatonin onset (DLMO) marks the beginning of nocturnal circadian activity. This prominent and reliable indicator corresponds to the first spike of melatonin synthesis and occurs in the early evening under low light conditions (Pandi-Perumal et al., 2007; Lewy et al., 1999).

Melatonin is essential for the normal regulation of sleep cycles in both diurnally and nocturnally active organisms, including humans. In humans, a significant urge in sleep tendency at night normally occurs two hours after the initiation of melatonin synthesis (Zisapel, 2018). The early evening rise in melatonin helps to trigger sleep onset while inhibition of melatonin secretion by bright evening light delays the rise in melatonin output. In addition to assisting with sleep onset, the duration of nocturnal melatonin activity serves to relay night length information to the brain, including the SCN, as well as to non-neural tissues. In both normally sighted and profoundly blind individuals, the circadian melatonin rhythm is closely linked to the sleep cycle. Other factors modify melatonin activity and these includes the effects of age, the presence of neurodegenerative disease, as well as certain pharmaceuticals (e.g., β-adrenoceptor blockers, clonidine, naloxone, and non-steroidal anti-inflammatory agents). These conditions or agents either reduce or abolish nocturnal melatonin synthesis and may

cause dysregulated sleep (Pandi-Perumal et al., 2008). In addition to promoting sleep onset and regulating circadian rhythms, melatonin, when it is administered exogenously, can benefit cardiovascular health and may slow cognitive decline in patients with Alzheimer's disease (Baltatu et al., 2019; Shukla et al., 2017). The observation that melatonin administration can reduce the normal suppression of the endogenous night signal has led to suggestions that this therapeutic approach could be of benefit for facilitating safe physical and mental aging (Srinivasan et al., 2009). It has been found that females tend to produce more melatonin than males, although the gender disparities in melatonin levels among elderly persons remain unclear (Obayashi et al., 2015). In a cross-sectional study (N=528; males=247; females=281), it was reported that the older females had significantly lower urinary melatonin excretion than older males (Obayashi et al., 2015). These findings thus underscore the importance of taking into consideration individual factors such as sex before initiating a program of melatonin supplement therapy (Olcese, 2020).

Disruption of these rhythms negatively impacts physical and mental health through its destabilizing effects on behavior, cognition, and mood (Albrecht, 2013; Bedrosian and Nelson, 2017; Benca et al., 2009; Richter, 1965; Schulz, 2007; Wirz-Justice,

2006). A large body of evidence has now established that chronic disruption of sleep and circadian rhythm can lead to the development of a number of physiological and psychiatric disorders (Karatsoreos, 2014; Melhuish Beaupre et al., 2018; Salgado-Delgado et al., 2011; Wirz-Justice, 2007, 2003). Zaki and coworkers reviewed evidence showing the importance of biological clock effects in mood disorders and depression (Zaki et al., 2018). Evidence from both animal model and epidemiological studies has shown that chronic circadian rhythm disturbance seems to raise the risk of metabolic diseases (Cardinali and Vigo, 2017; Karthikeyan et al., 2014; Reiter et al., 2012). It has been observed that time-restricted food intake activity without caloric restriction can promote and maintain greater metabolic homeostasis than such activity without restraints on time of food ingestion. This has led to the suggestion that such timing effects could be incorporated into a therapeutic strategy for managing metabolic disorders (Dashti et al., 2021).

Circadian rhythms play an integrative role in physiology and behavior, the clinical exploitation of which promises to have important utility for treatment (Panda, 2016). Evidence of circadian rhythm involvement in various physical and psychiatric disorders has been shown at multiple levels. Mice with a *Clock*

gene mutation exhibit behaviors that resemble the manic phase of human bipolar disorder. These have been shown to include hyperactivity, reduced sleep duration, and fewer behavioral symptoms of anxiety or depression (Roybal et al., 2007). Deletion of *Clock* genes in mice has been linked to oscillations of islet genes and subsequent disturbances in development, glucose metabolism, and insulin signaling. Again, these defects appear to be linked to genetic deficits in timing regulation. Mice with *Clock* and *Bmal1* mutations have compromised glucose resistance, decreased insulin secretion, and defects in pancreatic islet size. Further, these defects tend to proliferate and worsen with age (Marcheva et al., 2011). There is a strong association between sleep problems and ADHD, especially relative to sleep onset (Coogan et al., 2016). These are accompanied by a variety of rhythmic disruptions which can be detected physiologically, in, for instance, the endocrine system, as well as at the molecular and behavioral levels. Recent findings in these areas have suggested that phase advance techniques, currently used in sleep medicine to treat timing delays in circadian rhythms, may also help reduce symptoms of ADHD (Coogan et al., 2016). While having obvious applications in psychiatry, circadian realignment therapy could potentially be used for childhood developmental disorders which may be precursors to more serious problems in adulthood. Long-term

sleep restriction and circadian disruption in adolescent individuals have been shown to promote unhealthy behavioral activities and to increase the occurrence of substance use disorders (Logan et al., 2018).

Circadian Rhythm Sleep Disorders

Various sleep disturbances are strongly correlated with disruptions in circadian rhythms. The ICSD-3 (American Academy of Sleep Medicine, 2014) and DSM-5 (American Psychiatric Association, 2013) have classified circadian rhythm sleep disorders into several categories. The DSM-5 recognizes five disorders: delayed sleep-wake phase disorder (DSPS), advanced sleep-wake phase disorder (ASPS), non-24h sleep-wake disorder (N24SWD), irregular sleep-wake rhythm disorders (ISWRD), shift work disorder (SWD), and groups other disorders as parasomnias (Reynolds 3rd and O'Hara, 2013). The ICSD-3 also includes jet lag sleep disorders (JLD) (Sateia, 2014). Some of these disorders may be 'intrinsic', inasmuch as they are frequently chronic, familial, and related to genetic alterations. Extrinsic CRSDs, are triggered by environmental enforcement of an unfamiliar photoperiod (e.g. Jet Lag Disorder or JLD), work schedule (e.g. Shift-Work Disorder), or use of light emitting electronic devices(Duffy et al., 2021).

Insert Figure 2 about here

i

Diagnosis of circadian rhythm sleep-wake disorders

A recurrent or persistent pattern of sleep alteration, primarily due to changes in circadian regulation or a misalignment between the individual's internal body clock to geophysical LD cycle, and a sleep/wake pattern imposed separately by the schedule are required criteria for establishing the presence of a circadian rhythm sleep disorder. The disorder must also cause significant sleep disruption or distress in physical or social functioning. A further requirement is that the disruptions must be measurable. It is thus important to have quantified measures of the circadian phase (advance/delay; i.e. determining an alteration in the phase of the circadian rhythm), circadian peak, period length, and disruption of circadian oscillators is critical for delineating their function in sleep-wake disturbances (Dijk and Duffy, 2020). Traditionally, a precise assessment of the human circadian system has required extensive record keeping regarding, e.g., endogenous melatonin levels or core body temperatures, and it has been suggested that such protocols are often not clinically practical. As a consequence, alternative approaches for the assessment of circadian status are now being explored. These techniques, which are continuing to undergo development, utilize machine learning or use large datasets

obtained from the analysis of transcriptomes or metabolomes (Dijk and Duffy, 2020).

Delayed sleep phase syndrome (DSPS) is the most common occurring circadian rhythm sleep disorder (CRSD). An aberrant delay in the occurrence of a major sleep episode in proportion to the environmental zeitgeber is the most common symptom of this illness (Fahey and Zee, 2006; Nesbitt and Dijk, 2014). In some patients, a polymorphism in *Per3* has been discovered (Ebisawa et al., 2001). While in others, a variant in the *Cry1* gene has been discovered (Patke et al., 2017) however, most affected individuals have no known genetic abnormality. Many of the latter are adolescents and young adults who make extensive use of smartphones in the evening, a behavioral phenomenon so ubiquitous in modern-day life that it has been christened "cell phone addiction" (Gutiérrez et al., 2016). Recent evidence suggests that differences in endogenous period length (Micic et al., 2013) and/or light sensitivity (Abbott et al., 2020; Aoki et al., 2001; Watson et al., 2018) occur in this population.

The sleep phase in advanced sleep phase syndrome (ASPS) occurs unusually early in the evening compared to the night. Advanced sleep phase disorder (ASPD) patients have difficulties in remaining awake in the evenings and frequently fall asleep before completing personal and social tasks. Additionally, the

wake time of these patients is uncomfortably early and considered atypical in comparison to their peers. Several or all of these families share mutations that affect *Per2*, either in *CK1ε* or on *Per2*'s binding site (Toh et al., 2001; Zhang et al., 2016).

Non-24 h Sleep-Wake Phase Disorder (N24SWD) is a condition in which an individual's circadian clock does not synchronise to a 24 h day. As a result, patients' sleep-wake cycles typically display a gradual delay (usually minutes to hours), based on the circadian period of the individual. The timing of sleep gradually varies during a symptomatic phase, causing patients to suffer repeated bouts of daytime hypersomnolence and nighttime insomnia. The majority of individuals with N24SWD are entirely blind, although it can also affect people who have normal vision. Unlike the other CRSDs, a N24SWD diagnosis requires at least 14 days of consistent sleep/wake patterns, which are typically recorded using sleep diaries and/or actigraphy. Treatment of this disorder is very often successful with oral melatonin (Sack et al., 2000) or with the recently approved prescription medication Hetlioz® (tasimelteon, a melatonin analog) (Traynor, 2014).

Irregular sleep-wake disorder (ISWRD) is characterised by the absence of a discernible regular sleep-wake cycle and, as a result, the primary sleep episode lacks a temporal component.

Such irregular patterns have been reported in members of family groups with DSPD who also show mutations affecting CRY1 (Patke et al., 2017). It has been suggested that delay under restrictive environmental conditions could additionally cause symptoms of sleep fragmentation (Patke et al., 2017).

The American Academy of Sleep Medicine (AASM) guidelines for the management of circadian rhythm disorders have concluded that the most effective interventions can be broadly categorized into (1) Having a practice of regular sleep/wake schedule and/or physical activity/exercise, (2) Managing routine tasks with specific time and/or avoidance of sunlight & artificial light, (3) use of chronobiological agents altering or promoting sleep cycles; and (4) alternative therapies that influence sleep/wake habits by modifying bodily functions (i.e., somatic interventions) (Auger et al., 2015).

Circadian Draining of Brain Waste During Sleep

Recent theorizing suggested that a linkage may exist between sleep and the glymphatic system and that this relationship may serve an important rebalancing function. Homeostasis in the central nervous system, which requires an efficient elimination of metabolic waste products from the brain, exhibits circadian characteristics. This circadian control is manifested, for example, by the dependence of the

time of day on the permeability of the blood-brain barrier, demonstrated by the daily variation of the relative levels of metabolites between the CSF and the blood. The choroid plexus, which makes up an important part of the blood-CSF barrier, exhibits the rhythmicity of the circadian clock (Myung et al., 2018), regulating the exchange of fluids over time between blood and CSF. Glial cells of the hemolymph-brain barrier in fruit flies have a circadian clock that has been shown to regulate xenobiotic output (Zhang et al., 2018). These findings support the idea that astrocytic glial cells regulate the blood-brain barrier (BBB) and influence the clearance of metabolic waste in mammals.

Diffusion has long been used to explain solute changes in the extracellular space (ECS) of the central nervous system. It is now known that the process is somewhat more complex, with several local regulators such as adenosine, biogenic amines, NO, H+, and K+ working together to integrate blood flow and metabolism for the removal of waste products. More recently, and in parallel with conventional explanations for the process and function of removal of toxic products from the brain, a "glymphatic hypothesis", has been proposed. This model emphasizes the importance of active lymphatic-like movements in the cerebral ECS (Boespflug and Iliff, 2018; Iliff et al., 2013, 2012; Jessen et al., 2015). Although the CNS lacks lymphatic

vessels, it has been suggested that this process may nevertheless take place in the brain due to water exchange driven by aquaporin-4 (AQP4). The vascular lumen is altered by the passage of solute matter in perivascular astrocytes, which have high concentrations of Aquaporin-4 (AQP4). The AQP4 water channel is found mostly in the foot processes of astrocytes. The release of water through AQP4 may account for an actively guided exchange of fluid between the periarterial and perivenous spaces, which are linked in other areas of the ECS, such as the interstitial fluid, by the convective flow. Furthermore, it has been hypothesized that pulsation by arterioles, together with respiration-dependent venous collapse, may further increase this flow (Nedergaard, 2013).

Sleep, in particular NREM sleep, is strongly associated with the removal of brain waste (Boespflug and Iliff, 2018; Iliff et al., 2013, 2012; Jessen et al., 2015). An example is the elimination of amyloid peptide β (Aβ), which improves significantly during sleep. The discovery that clearance of injected radio-labelled Aβ peptide is considerably decreased in AQP4 - / - mice lends support to the idea of Aβ glymphatic clearance (Iliff et al., 2012). Inasmuch as during NREM sleep the cortical interstitial space expands by >60%, solute exchange between CSF and interstitial fluid (ISF) is at its maximum, and thus presents only limited resistance to CSF and ISF movement

during this sleep stage. The glymphatic system's contribution to the sleep repair mechanism is strongly reliant on age-related sleep profiles. Sleep among elderly subjects is associated with delayed and decreased fluid entry into the CSF along the perivascular tract and the pial wall (Zeppenfeld et al., 2017). Glymphatic system dysfunction is also visible in several neurological conditions, including Alzheimer's disease (AD), traumatic brain injury (TBI), and stroke (Boespflug and Iliff, 2018). Taken together, these findings show that the circadian clock and the REM/NREM cycle control many critical processes in the brain. Among other activities, these include the maintenance of regulated trafficking of substances into and out of the brain, brain metabolism, and sleep/wake control. Any tampering of the circadian clock and pathways may result in inefficient and dysregulated metabolic processes (Albrecht and Ripperger, 2018).

The impact of sex related variables on variations in sleep and circadian rhythms

The challenge of identifying how sleep is affected by circadian regulation, and more importantly about the consequences of disruptions to this regulation, is further complicated by how these processes are differentially affected in men and women. Men and women have differential responses in

hypothalamic-pituitary-gonadal (HPG) axis, hypothalamic-adrenal-pituitary (HPA) axis, and sleep-arousal systems. Understanding how these systems' circadian rhythms are disrupted differs by sex and is associated with malfunction and disease. Understanding sex-specific circadian timing mechanisms may lead to more effective treatments for these illnesses (Bailey and Silver, 2014). Sexual differences in sleeping patterns have been underemphasized in experimental designs. Women in human studies and females in animal studies have always been historically underrepresented in research studies (Feldman et al., 2019), circadian and sleep-related studies are no exception.

In both basic and clinical research studies, sexual variations in normal and pathological sleep have been identified globally (Anderson and FitzGerald, 2020; Jonasdottir et al., 2021; Tang et al., 2017; Krishnan and Collop, 2006). Sleep characteristics such as sleep timing and quality are significantly influenced by age and sex (Li et al., 2021; Madrid-Valero et al., 2017). Females have a higher frequency of sleep difficulties than males, according to various surveys (Madrid-Valero et al., 2017; Stranges et al., 2012; Suzuki et al., 2015; Uhlig et al., 2014; Zhang and Wing, 2006; Ishigooka et al., 1999). The prevalence of insomnia increases with age, as reported in most population-based research undertaken in a

number of countries (Kerkhof et al., 2017; Leng et al., 2014; Ohayon et al., 2004; Middelkoop et al., 1996; Reyner et al., 1995). When compared to men, women of all ages report having sleep that is of poorer quality, more fragmented, and less satisfying (Tsai and Li, 2004). Some reviews have suggested that studies of sleep disorders among college students and other groups have suffered from a failure to properly account for how these problems manifest in males and females (Galambos et al., 2009; Carney et al., 2006). In a meta-analysis of the pooled prevalence study in the general population of China (N=115,988), no significant differences were found in the prevalence of insomnia between men and women (Cao et al., 2017). In another study, variations in the circadian amplitude of plasma melatonin and electroencephalographic (EEG) slow-wave activity (SWA) could not explain the sex differences in cognitive regulation (Santhi et al., 2016). Taken together, these research deficiencies point to the presence of a limited appreciation among many researchers for how sex differences can affect sleep and circadian regulation.

Another phenomenon which has been documented to affect circadian rhythms is shift work. There is growing evidence that suggests that the female shift employees are more likely than male shift workers to complain about sleep disorders, and

they have more trouble initiating and maintaining sleep after work. Hence, impairments in the quantity and quality of sleep are greater among women than men, and they report greater difficulties in adjusting to shift work as compared to their male counterparts (Chung et al., 2009; Admi et al., 2008). Night shift work contributes to a greater prolongation of pregnancy, reduces fetal growth in industrial shift workers, and increases the requirement for fertility therapy in young women (Fernandez et al., 2020; Zhu et al., 2004). Clinical and basic research findings point to the importance of of sex steroids in sleep modulation, as well as to how neuroendocrine mediators and sex variables influence sleep (Mong and Cusmano, 2016). Sleep health providers should be aware of these discrepancies at all levels of disease prevention and health promotion to improve the quality of life for people with sleep-related health concerns. These include the diagnosis, treatment, management, and patient education (Boccabella and Malouf, 2017).

There are still major information gaps in research with respect to the sleep of men and women. More basically, there continues to be a general lack of awareness among the scientific community that many studies have frequently failed to include females in their experimental designs (Mallampalli and Carter, 2014). These deficits indicate that considerable work remains to

be carried out to explicate the impact of sex related differences on sleep disorders (Mallampalli and Carter, 2014), and more specifically suggest that future sleep studies should include more females. It is essential for the requirements of evidence based medicine, and especially for the creation of targeted therapy programs, that research on sleep disorders take sex related biological differences into account.

Conclusion

The discipline of sleep medicine has advanced significantly since the pioneering sleep investigations of Dement and Kleitman (1957), Jouvet and Courjon (1959), and Rechtschaffen et al (1966). It could be argued that, in terms of research and acknowledgment by the broader scientific community, the importance of circadian rhythms to overall health is now more fully appreciated. Despite the growing evidence for its efficacy, chronomedicine or chronotherapy (i.e. timed administration of a drug or other interventions according to the patient's biological clock) is still under-researched and under-utilized. For example, the use of light therapy, dark therapy, blue-blocking lenses, wake therapy, and effective utilization of chronobiotic substances such as melatonin and its derivatives. More research and clinical applications for chronotherapy are

hoped to result from the growing awareness of the significance of circadian rhythms in both sleep and overall health.

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Authors' Contribution

All authors met the ICMJE criteria for authorship. All authors contributed equally in the subsequent preparation of the manuscript. SRP, DPC, RJR, GMB conceived and designed the

outline of review; NFWZ, RK performed the literature search; SRP, DPC, RK wrote the paper; NFWZ, DWS, RJR, GMB performed critical review of the initial and/or copy edit the subsequent drafts; and all authors (SRP, DPC, NFWZ, RK, DWS, RJR, GMB) approved the final version of the manuscript prior to the submission.

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References

Abbott, S.M., Malkani, R.G., Zee, P.C., 2020. Circadian disruption and human health: A bidirectional relationship. Eur. J. Neurosci. 51(1):567-583. https://doi.org/10.1111/ejn.14298

Admi, H., Tzischinsky, O., Epstein, R., Herer, P., Lavie, P., 2008. Shift work in nursing: is it really a risk factor for nurses' health and patients' safety? Nurs Econ. 26(4):250-7. PMID: 18777974.

Aeschbach, D., Cajochen, C., Landolt, H., Borbely, A.A., 2017. Homeostatic sleep regulation in habitual short sleepers and long sleepers. Am. J. Physiol. Integr. Comp. Physiol. 270, R41–R53. https://doi.org/10.1152/ajpregu.1996.270.1.r41

Albrecht, U., 2013. Circadian Clocks and Mood-Related Behaviors, in: Handbook of Experimental Pharmacology. Handb Exp Pharmacol, pp. 227–239. https://doi.org/10.1007/978-3-642-25950-0_9

Albrecht, U., Ripperger, J.A., 2018. Circadian Clocks and Sleep: Impact of Rhythmic Metabolism and Waste Clearance on the Brain. Trends Neurosci. 41(10):677-688. https://doi.org/10.1016/j.tins.2018.07.007

American Academy of Sleep Medicine. International classification of Sleep Disorders, 3rd edn. American Academy of Sleep Medicine, Darien, IL, 2014.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th edn. American Psychiatric Publishing, Arlington, VA, 2013.

Anderson, S.T., Fitzgerald, G.A.,2020. Sexual dimorphism in body clocks. Science 369(6508):1164-1165. DOI: 10.1126/science.abd4964.

Aoki, H., Ozeki, Y., Yamada, N., 2001. Hypersensitivity of melatonin suppression in response to light in patients with delayed sleep phase syndrome. Chronobiol. Int. 18, 263–271. https://doi.org/10.1081/CBI-100103190

Archer, S.N., Schmidt, C., Vandewalle, G., Dijk, D.J., 2018. Phenotyping of PER3 variants reveals widespread effects on circadian preference, sleep regulation, and health. Sleep Med. Rev. 40:109-126.

https://doi.org/10.1016/j.smrv.2017.10.008

Aschoff, J., 1965. Circadian rhythms in man. Science 148(3676):1427-32. https://doi.org/10.1126/science.148.3676.1427

Aston-Jones, G., Bloom, F.E., 1981. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J. Neurosci. 1, 876–886. doi: 10.1523/JNEUROSCI.01-08-00876.1981.

Atkinson, G., Edwards, B., Reilly, T., Waterhouse, J., 2007. Exercise as a synchroniser of human circadian rhythms: an update and discussion of the methodological problems. Eur. J. Appl. Physiol. 99, 331–341. doi: 10.1007/s00421-006-0361-z.

Auger, R.R., Burgess, H.J., Emens, J.S., Deriy, L. V, Thomas, S.M., Sharkey, K.M., 2015. Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders. J. Clin. Sleep Med. 11, 1199–236. https://doi.org/10.5664/jcsm.5100

Bailey, M., Silver, R. Sex differences in circadian timing systems: implications for disease. Front Neuroendocrinol. 2014 Jan;35(1):111-39. doi: 10.1016/j.yfrne.2013.11.003.

Baltatu, O.C., Senar, S., Campos, L.A., Cipolla-Neto, J., 2019. Cardioprotective melatonin: Translating from proof-of-concept studies to therapeutic use. Int. J. Mol. Sci. https://doi.org/10.3390/ijms20184342

Bedrosian, T.A., Nelson, R.J., 2017. Timing of light exposure affects mood and brain circuits. Transl. Psychiatry Transl Psychiatry. 7(1): e1017. doi: 10.1038/tp.2016.262.

Benedetti, F., Serretti, A., Colombo, C., Barbini, B., Lorenzi, C., Campori, E. and Smeraldi, E., 2003. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 123(1), pp.23-26.

Benca, R., Duncan, M.J., Frank, E., McClung, C., Nelson, R.J., Vicentic, A., 2009. Biological rhythms, higher brain function, and behavior: Gaps, opportunities, and challenges. Brain Res Rev. 2009 Dec 11;62(1):57-70. doi: 10.1016/j.brainresrev.2009.09.005.

Blouin, A.M., Fried, I., Wilson, C.L., Staba, R.J., Behnke, E.J., Lam, H.A., Maidment, N.T., Karlsson, K., Lapierre,

J.L., Siegel, J.M., 2013. Human hypocretin and melanin-concentrating hormone levels are linked to emotion and social interaction. Nat Commun. 2013;4:1547. doi: 10.1038/ncomms2461.

Blume, C., Garbazza, C., Spitschan, M., 2019. Effects of light on human circadian rhythms, sleep and mood. Somnologie (Berl). 23(3):147-156. doi: 10.1007/s11818-019-00215-x.

Boccabella, A., Malouf, J., 2017. How Do Sleep-Related Health Problems Affect Functional Status According to Sex? J Clin Sleep Med. 13(5): 685–692. doi: 10.5664/jcsm.6584.

Boes, A.D., Fischer, D., Geerling, J.C., Bruss, J., Saper, C.B., Fox, M.D., 2018. Connectivity of sleep- and wake-promoting regions of the human hypothalamus observed during resting wakefulness. Sleep 41. https://doi.org/10.1093/sleep/zsy108

Boespflug, E.L., Iliff, J.J., 2018. The Emerging Relationship Between Interstitial Fluid–Cerebrospinal Fluid Exchange, Amyloid-β and Sleep. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2017.11.031

Boivin, D. B., Duffy, J. F., Kronauer, R. E., & Czeisler, C. A. (1996). Dose-response relationships for resetting of human circadian clock by light. Nature, 379(6565), 540-542. doi: 10.1038/379540a0.

Borb, A.A., Achermann, P., 1999. Sleep Homeostasis and Models of Sleep Regulation. J. Biol. Rhythms 14, 559–570. https://doi.org/10.1177/074873099129000894

Borbely, A.A., 1982. A two process model of sleep regulation. Hum Neurobiol 1, 195–204. PMID: 7185792.

Borbély, A.A., Daan, S., Wirz-Justice, A., Deboer, T., 2016. The two-process model of sleep regulation: A reappraisal. J. Sleep Res. 25, 131–143. https://doi.org/10.1111/jsr.12371

Bracci, M., Manzella, N., Copertaro, A., Staffolani, S., Barbaresi, I.M., Strafella, E., Copertaro, B., Rapisarda, V., Valentino, M., Santarelli, L., 2014. Rotating-shift nurses after a day off: Peripheral clock gene expression, urinary melatonin, and serum 17-β-estradiol levels. Scand. J. Work. Environ. Heal. 40, 295–304. https://doi.org/10.5271/sjweh.3414.

Cain, S.W., Dennison, C.F., Zeitzer, J.M., Guzik, A.M., Khalsa, S.B.S., Santhi, N., Schoen, M.W., Czeisler, C.A., Duffy, J.F., 2010. Sex differences in phase angle of entrainment and

melatonin amplitude in humans. J Biol Rhythms. 25(4):288-96. doi: 10.1177/0748730410374943.

Cao, X.L., Wang, S.B., Zhong, B.L., Zhang, L., Ungvari, G.S., Ng, C.H., Li, L., Chiu, H.F.K., Lok, G.K.I., Lu, J.P., Jia, F.J., Xiang, Y.T., 2017. The prevalence of insomnia in the general population in China: A meta-analysis. PLoS One. 12(2):e0170772. doi: 10.1371/journal.pone.0170772.

Cardinali, D.P., Bortman, G.P., Liotta, G., Lloret, S.P., Albornoz, L.E., Cutrera, R.A., Batista, J., Gallo, P.O., 2002. A multifactorial approach employing melatonin to accelerate resynchronization of sleep-wake cycle after a 12 time-zone westerly transmeridian flight in elite soccer athletes. J. Pineal Res. 32(1):41-6. https://doi.org/10.1034/j.1600-079x.2002.10820.x

Cardinali, D.P., Vigo, D.E., 2017. Melatonin, mitochondria, and the metabolic syndrome. Cell. Mol. Life Sci. 74(21):3941-3954. https://doi.org/10.1007/s00018-017-2611-0

Carney, C.E., Edinger, J.D., Meyer, B., Lindman, L., Istre, T., 2006. Daily activities and sleep quality in college students. Chronobiol Int 23:623–37. doi: 10.1080/07420520600650695.

Chang, A. M., Aeschbach, D., Duffy, J. F., & Czeisler, C. A., 2015. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. Proc Natl Acad Sci U S A. 112(4):1232-7.

Chang, A. M., Scheer, F. A., & Czeisler, C. A., 2011. The human circadian system adapts to prior photic history. The Journal of physiology, 589(5), 1095-1102.

Charrier, A., Olliac, B., Roubertoux, P., Tordjman, S., 2017. Clock genes and altered sleep–wake rhythms: Their role in the development of psychiatric disorders. Int. J. Mol. Sci. 18(5):938. https://doi.org/10.3390/ijms18050938

Chung, S.A., Wolf, T.K., Shapiro, C.M., 2009. Sleep and health consequences of shift work in women. J Womens Health (Larchmt). 18(7):965-77. doi: 10.1089/jwh.2007.0742.

Colwell, C.S., Michel, S., 2003. Sleep and circadian rhythms: Do sleep centers talk back to the clock? Nat. Neurosci. 6(10): 1005–1006. https://doi.org/10.1038/nn1003-1005.

Coogan, A.N., Baird, A.L., Popa-Wagner, A., Thome, J., 2016.

Circadian rhythms and attention deficit hyperactivity disorder: The what, the when and the why. Prog. Neuro-Psychopharmacology Biol. Psychiatry. 67:74-81. https://doi.org/10.1016/j.pnpbp.2016.01.006

Cox, K.H., Takahashi, J.S., 2019. Circadian Clock Genes and the Transcriptional Architecture of the Clock Mechanism. J Mol Endocrinol. 63(4): R93–R102. doi: 10.1530/JME-19-0153.

Czeisler, C.A., Kronauer, R.E., Allan, J.S., Duffy, J.F., Jewett, M.E., Brown, E.N., Ronda, J.M., 1989. Bright light induction of strong (type 0) resetting of the human circadian pacemaker. Science 244(4910):1328-33. doi: 10.1126/science.2734611.

Dacey, D.M.., Liao, H.-W., Peterson, B.B.., Robinson, F.R.., Smith, V.C.., Pokorny, J., Yau, K.-W., Gamlin, P.D., 2005. Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. Nature 433, 749–754. https://doi.org/10.1038/nature03387.

Dai, J., Van Der Vliet, J., Swaab, D.F., Buijs, R.M., 1998. Human retinohypothalamic tract as revealed by in vitro postmortem tracing. J. Comp. Neurol. 397(3):357-70. https://doi.org/10.1002/(SICI)1096-9861(19980803)397:3<357::AID-CNE4>3.0.CO;2-1

Dashti, H.S., Gómez-Abellán, P., Qian, J., Esteban, A., Morales, E., Scheer, F.A.J.L., Garaulet, M., 2021. Late eating is associated with cardiometabolic risk traits, obesogenic behaviors, and impaired weight loss. Am. J. Clin. Nutr. 113, 154–161. https://doi.org/10.1093/ajcn/nqaa264

de Souza Teixeira, A.A., Lira, F.S., Rosa-Neto, J.C., 2020. Aging with rhythmicity. Is it possible? Physical exercise as a pacemaker. Life Sci. 261:118453. doi: 10.1016/j.lfs.2020.118453.

Deboer, T., 2018. Sleep homeostasis and the circadian clock: Do the circadian pacemaker and the sleep homeostat influence each other's functioning? Neurobiol. Sleep Circadian Rhythm. 5:68-77. https://doi.org/10.1016/j.nbscr.2018.02.003.

Deboer, T., Vansteensel, M.J., Détári, L., Meijer, J.H., 2003. Sleep states alter activity of suprachiasmatic nucleus neurons. Nat. Neurosci. 6, 1086–1090. https://doi.org/10.1038/nn1122

Dement, W., Kleitman, N., 1957. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and

i

dreaming. Electroencephalogr. Clin. Neurophysiol. 9, 673–690. https://doi.org/10.1016/0013-4694(57)90088-3

Dijk, D.J., Duffy, J.F., 2020. Novel Approaches for Assessing Circadian Rhythmicity in Humans: A Review. J. Biol. Rhythms. 35(5):421-438. doi: 10.1177/0748730420940483.

Dijk, D.J., Lockley, S.W., 2002. Invited review: Integration of human sleep-wake regulation and circadian rhythmicity. J. Appl. Physiol. 92, 852–862. https://doi.org/10.1152/japplphysiol.00924.2001

Duffy, J.F., Abbott, S.M., Burgess, H.J., Crowley, S.J., Emens, J.S., Epstein, L.J., Gamble, K.L., Hasler, B.P., Kristo, D.A., Malkani, R.G., Rahman, S.A., Thomas, S.J., Wyatt, J.K., Zee, P.C., Klerman, E.B., 2021. Workshop report. Circadian rhythm sleep–wake disorders: gaps and opportunities. Sleep. 44(5): zsaa281. https://doi.org/10.1093/sleep/zsaa281

Duffy, J.F., Cain, S.W., Chang, A.M., Phillips, A.J.K., Münch, M.Y., Gronfier, C., Wyatt, J.K., Dijk, D.J., Wright Jr., K.P., Czeisler, C.A., 2011. Sex difference in the near-24-hour intrinsic period of the human circadian timing system. PNAS 108 (Supplement 3) 15602-15608. https://doi.org/10.1073/pnas.1010666108.

Easton, A., Meerlo, P., Bergmann, B., Turek, F.W., 2004. The suprachiasmatic nucleus regulates sleep timing and amount in mice. Sleep 27, 1307–1318. https://doi.org/10.1093/sleep/27.7.1307

Eban-Rothschild, A., Bloch, G., 2012. Social Influences on Circadian Rhythms and Sleep in Insects. Adv Genet. 77:1-32. doi: 10.1016/B978-0-12-387687-4.00001-5.

Ebisawa, T., Uchiyama, M., Kajimura, N., Mishima, K., Kamei, Y., Katoh, M., Watanabe, T., Sekimoto, M., Shibui, K., Kim, K., Kudo, Y., Ozeki, Y., Sugishita, M., Toyoshima, R., Inoue, Y., Yamada, N., Nagase, T., Ozaki, N., Ohara, O., Ishida, N., Okawa, M., Takahashi, K., Yamauchi, T., 2001. Association of structural polymorphisms in the human period3 gene with delayed sleep phase syndrome. EMBO Rep. 2(4): 342–346. doi: 10.1093/embo-reports/kve070

Emens, J.S., 2017. Circadian Rhythms: The Price of Electric Light. Curr. Biol. 27(4):R144-R145. doi: 10.1016/j.cub.2017.01.014.

Esquiva, G., Lax, P., Pérez-Santonja, J.J., García-Fernández, J.M., Cuenca, N., 2017. Loss of melanopsin-expressing

ganglion cell subtypes and dendritic degeneration in the aging human retina. Front. Aging Neurosci. 9:79. doi: 10.3389/fnagi.2017.00079.

Fahey, C.D., Zee, P.C., 2006. Circadian rhythm sleep disorders and phototherapy. Psychiatr. Clin. North Am. 29, 989–1007. doi: 10.1016/j.psc.2006.09.009

Feldman, F., Ammar, W., Lo, K., Trepman, E., van Zuylen, M., Etzioni, O., 2019.Quantifying Sex Bias in Clinical Studies at Scale With Automated Data Extraction. JAMA Netw Open. 2(7):e196700. doi: 10.1001/jamanetworkopen.2019.6700.

Fernandez, F. Circadian Responses to Fragmented Light: Research Synopsis in Humans. Yale J Biol Med. 2019 Jun 27;92(2):337-348. PMID: 31249494.

Fernandez, R.C., Moore, V.M., Marino, J.L., Whitrow, M.J., Davies, M.J., 2020. Night Shift Among Women: Is It Associated With Difficulty Conceiving a First Birth? Front Public Health. 8: 595943. doi: 10.3389/fpubh.2020.595943.

Figueiro, M.G., 2013. An Overview of the Effects of Light on Human Circadian Rhythms: Implications for New Light Sources and Lighting Systems Design. Journal of Light & Visual Environment, 37(2_3), 51–61. doi:10.2150/jlve.ieij130000503.

Foster, R.G., 2020. Sleep, circadian rhythms and health. Interface Focus. 10(3):20190098. doi: 10.1098/rsfs.2019.0098.

Frank, J., Gupta, A., Osadchiy, V., Mayer, E.A., 2021. Brain-Gut-Microbiome Interactions and Intermittent Fasting in Obesity. Nutrients 13(2):584. doi: 10.3390/nu13020584.

Franken, P., Dijk, D.J., 2009. Circadian clock genes and sleep homeostasis. Eur J Neurosci. 29(9):1820-9. doi: 10.1111/j.1460-9568.2009.06723.x

Fulcher, B.D., Phillips, A.J.K., Postnova, S., Robinson, P.A., 2014. A physiologically based model of orexinergic stabilization of sleep and wake. PLoS One. 29(3):e91982. doi: 10.1371/journal.pone.0091982

Fuller, P.M., Gooley, J.J., Saper, C.B., 2006. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. J Biol Rhythms. 21(6):482-93. doi: 10.1177/0748730406294627

Galambos, N.L., Dalton, A.L., Maggs, J.L. 2009. Losing sleep over it: daily variation in sleep quantity and quality in

Canadian students' first semester of university. J Res Adolesc 19:741–61. https://doi.org/10.1111/j.1532-7795.2009.00618.x

Gooley, J.J., 2017. Light-induced Resetting of Circadian Rhythms in Humans. J. Sci. Technol. Light. 41, 69–76. https://doi.org/10.2150/jstl.ieij160000594

Gooley, J.J., Chamberlain, K., Smith, A.K., Khalsa, S.B.S., Rajaratnam, S.M.W., Van Reen, E, Zeitzer, J.M., Czeisler, C.A., Lockley, S.W., 2011. Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. J Clin Endocrinol Metab. 96(3):E463-72. doi: 10.1210/jc.2010-2098.

Gooley, J.J., Lu, J., Fischer, D., Saper, C.B., 2003. A broad role for melanopsin in nonvisual photoreception. J. Neurosci. 23, 7093–7106. https://doi.org/10.1523/jneurosci.23-18-07093.2003

Gronfier, C., Wright, K. P., Kronauer, R. E., Czeisler, C. A., 2007. Entrainment of the human circadian pacemaker to longer-than-24-h days. Proc Natl Acad Sci U S A. 104(21):9081-6. doi: 10.1073/pnas.0702835104.

Grubisic, M., Haim, A., Bhusal, P., Dominoni, D.M., Gabriel, K.M.A., Jechow, A., Kupprat, F., Lerner, A., Marchant, P., Riley, W., Stebelova, K., van Grunsven, R.H.A., Zeman, M., Zubidat, A.E., Hölker, F., 2019. Light Pollution, Circadian Photoreception, and Melatonin in Vertebrates. Sustainability. 11(22):6400. https://doi.org/10.3390/su11226400

Gunn, P.J., BMiddleton, B., Davies, S.K., Revell, V.L., Skene, D.J., 2016. Sex differences in the circadian profiles of melatonin and cortisol in plasma and urine matrices under constant routine conditions. Chronobiol Int. 33(1):39-50. doi: 10.3109/07420528.2015.1112396.

Gutiérrez, J.D.S., de Fonseca, F.R., Rubio, G., 2016. Cell-phone addiction: A review. Front Psychiatry. 7: 175. doi: 10.3389/fpsyt.2016.00175

Halberg, F., Peterson, R.E., Silber, R.H., 1959. Phase relations of 24-hour periodicities in blood corticosterone, mitoses in cortical adrenal parenchyma, and total body activity. Endocrinology 64, 222–230. https://doi.org/10.1210/endo-64-2-222

Hannibal, J., Christiansen, AT; Heegaard, S., Fahrenkrug, J.,

Kiilgaard, J., 2017. Melanopsin containg human retinal ganglion cells: Subtypes, distribution, and intraretinal connectivity. J Comp Neurol. 525(8):1934-1961. doi: 10.1002/cne.24181

Hassani, O.K., Pablo, H., Lee, M.G., Jones, B.E., 2011. GABAergic neurons intermingled with orexin and MCH neurons in the Lateral Hypothalamus Discharge Maximally During Sleep. Eur J Neurosci. 32, 448–457. https://doi.org/10.1111/j.1460-9568.2010.07295.x.GABAergic

Hastings, M.H., Maywood, E.S., Brancaccio, M., 2018. Generation of circadian rhythms in the suprachiasmatic nucleus. Nat Rev Neurosci.19(8):453-469. doi: 10.1038/s41583-018-0026-z

Honma, K.I., Hashimoto, S., Nakao, M., Honma, S., 2003. Period and phase adjustments of human circadian rhythms in the real world. J Biol Rhythms. 18(3):261-70. doi: 10.1177/0748730403018003008

Iliff, J.J., Lee, H., Yu, M., Feng, T., Logan, J., Nedergaard, M., Benveniste, H., 2013. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. J. Clin. Invest. 123, 1299–1309. https://doi.org/10.1172/JCI67677

Iliff, J.J., Wang, M., Liao, Y., Plogg, B.A., Peng, W., Gundersen, G.A., Benveniste, H., Vates, G.E., Deane, R., Goldman, S.A., Nagelhus, E.A., Nedergaard, M., 2012. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci. Transl. Med. Vol. 4(147): 147ra111. https://doi.org/10.1126/scitranslmed.3003748

Inouye, S.T., Kawamura, H., 1979. Persistence of circadian rhythmicity in a mammalian hypothalamic “island” containing the suprachiasmatic nucleus. Proc. Natl. Acad. Sci. U. S. A. 76, 5962–5966. https://doi.org/10.1073/pnas.76.11.5962

Ishigooka, J., Suzuki, M., Isawa, S., Muraoka, H., Murasaki, M., Okawa, M., 2017. Epidemiological study on sleep habits and insomnia of new outpatients visiting general hospitals in Japan. Psychiatry Clin Neurosci. 1999 Aug;53(4):515-22. doi: 10.1046/j.1440-1819.1999.00578.x. Kerkhof, G. A. Epidemiology of sleep and sleep disorders in Te Netherlands. Sleep Med. 30, 229–239. https://doi.org/10.1016/j.sleep.2016.09.015

Jehan, S., Jean-Louis, G., Zizi, F., Auguste, E., Pandi-Perumal, S.R., Gupta, R., Attarian, H., McFarlane, S.I., Hardeland,

R., Brzezinski, A. 2017. Sleep, Melatonin, and the Menopausal Transition: What Are the Links? Sleep Sci. 10(1): 11–18. doi: 10.5935/1984-0063.20170003.

Jessen, N.A., Munk, A.S.F., Lundgaard, I., Nedergaard, M., 2015. The Glymphatic System: A Beginner's Guide. Neurochem. Res. 40, 2583–2599. https://doi.org/10.1007/s11064-015-1581-6

Jonasdottir, S.S., Minor, K., Lehmann, S., 2021. Gender differences in nighttime sleep patterns and variability across the adult lifespan: a global-scale wearables study. Sleep. 44(2):zsaa169. doi: 10.1093/sleep/zsaa169.

Jones, B., 2019. Arousal and sleep circuits. Neuropsychopharmacology 45(1):6-20. doi: 10.1038/s41386-019-0444-2.

Jones, B.E., Hassani, O.K., 2013. The role of hcrt/orx and MCH neurons in sleep-wake state regulation. Sleep 36, 1769–1772. https://doi.org/10.5665/sleep.3188

Jouvet, M., 1972. The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle. Ergeb. Physiol. 64, 166–307. https://doi.org/10.1007/3-540-05462-6_2

Jouvet, M., Michel, F., Courjon, J., 1959. Sur un stade d'activité électrique cérébrale rapide au cours du sommeil physiologique. Comptes rendus des séances de l'Académie des Sciences 6:1024.

Karatsoreos, I.N., 2014. Links between circadian rhythms and psychiatric disease. Front. Behav. Neurosci. 8: 162. https://doi.org/10.3389/fnbeh.2014.00162

Karthikeyan, R., Marimuthu, G., Ramasubramanian, C., Arunachal, G., BaHammam, A.S., Spence, D.W., Cardinali, D.P., Brown, G.M. and Pandi-Perumal, S.R., 2014. Association of Per3 length polymorphism with bipolar I disorder and schizophrenia. Neuropsychiatr Dis Treat. 10:2325-30. doi: 10.2147/NDT.S73765.

Karthikeyan, R., Marimuthu, G., Spence, D.W., Pandi-Perumal, S.R., BaHammam, A.S., Brown, G.M., Cardinali, D.P., 2014. Should we listen to our clock to prevent type 2 diabetes mellitus? Diabetes Res. Clin. Pract. 106(2):182-90. doi: 10.1016/j.diabres.2014.07.029.

Kim, Y.H., Lazar, M.A., 2020. Transcriptional Control of Circadian Rhythms and Metabolism: A Matter of Time and Space.

Endocr Rev. 41(5): 707–732. doi: 10.1210/endrev/bnaa014

Kinoshita, C., Okamoto, Y., Aoyama, K., Nakaki, T., 2020. MicroRNA: A Key Player for the Interplay of Circadian Rhythm Abnormalities, Sleep Disorders and Neurodegenerative Diseases. Clocks & Sleep 2, 282–307. https://doi.org/10.3390/clockssleep2030022

Kissling, C., Retz, W., Wiemann, S., Coogan, A.N., Clement, R.M., Hunnerkopf, R., Conner, A.C., Freitag, C.M., Rosler, M., Thome, J., 2008. A polymorphism at the 3'- untranslated region of the CLOCK gene is associated with adult attention-deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet. 147(3):333-8. doi: 10.1002/ajmg.b.30602.

Klein, D.C., Moore, R.Y., 1979. Pineal N-acetyltransferase and hydroxyindole-O-methyltransferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus. Brain Res. 174(2):245-62. doi: 10.1016/0006-8993(79)90848-5.

Klerman, E.B., Dijk, D.J., Kronauer, R.E., Czeisler, C.A., 1996. Simulations of light effects on the human circadian pacemaker: implications for assessment of intrinsic period. Am J Physiol. 270(1 Pt 2):R271-82. doi: 10.1152/ajpregu.1996.270.1.R271.

Krishnan, V., Collop, N.A., 2006. Gender differences in sleep disorders. Curr Opin Pulm Med. 12(6):383-9. doi: 10.1097/01.mcp.0000245705.69440.6a.

Kronauer, R., 1990. A quantitative model for the effects of light on the amplitude and phase of the deep circadian pacemaker based on human data, in: Horne, J. (Ed.), Sleep, 90. Pontenagel, Bochum, Germany., pp. 306–309.

Lavie, P., 2001. Sleep-wake as a biological rhythm. Annu. Rev. Psychol. 52, 277–303. https://doi.org/10.1146/annurev.psych.52.1.277

Lazar, A.S., Lazar, Z.I., Dijk, D.J., 2015. Circadian regulation of slow waves in human sleep: Topographical aspects. Neuroimage 116, 123–134. https://doi.org/10.1016/j.neuroimage.2015.05.012

Leng, Y., Wainwright, N.W.J., Cappuccio, F.P., Surtees, P.G., Luben, R., Wareham, N., Brayne, C., Khaw, K.T., 2014. Self-reported sleep patterns in a British population cohort. Sleep Med. 15(3):295-302. doi: 10.1016/j.sleep.2013.10.015.

Lewy, A.J., Cutler, N.L., Sack, R.L., 1999. The endogenous melatonin profile as a marker for circadian phase position. J Biol Rhythms. 14(3):227-36. doi: 10.1177/074873099129000641

Li, J.Z., Bunney, B.G., Meng, F., Hagenauer, M.H., Walsh, D.M., Vawter, M.P., Evans, S.J., Choudary, P.V., Cartagena, P., Barchas, J.D., Schatzberg, A.F., Jones, E.G., Myers, R.M., Watson, S.J. Jr., Akil, H., Bunney, W.E., 2013. Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. Proc Natl Acad Sci U S A. 110(24):9950-5. doi: 10.1073/pnas.1305814110.

Li, L., Nakamura, T., Hayano, J. Yamamoto, Y., 2021. Age and gender differences in objective sleep properties using large-scale body acceleration data in a Japanese population. Sci Rep 11, 9970. https://doi.org/10.1038/s41598-021-89341-x

Lim, A.S.P., Myers, A.J., Yu, L., Buchman, A.S., Duffy, J.F., De Jager, P.L., Bennett, D.A., 2013. Sex difference in daily rhythms of clock gene expression in the aged human cerebral cortex. J Biol Rhythms. 2013 Apr;28(2):117-29. doi: 10.1177/0748730413478552.

Logan, R.W., Hasler, B.P., Forbes, E.E., Franzen, P.L., Torregrossa, M.M., Huang, Y.H., Buysse, D.J., Clark, D.B., McClung, C.A., 2018. Impact of Sleep and Circadian Rhythms on Addiction Vulnerability in Adolescents. Biol Psychiatry. 283(12):987-996. doi: 10.1016/j.biopsych.2017.11.035 https://doi.org/10.1016/j.biopsych.2017.11.035

Madrid-Valero, J.J., Martínez-Selva, J.M., Ribeiro do Couto, B., Sánchez-Romera, J.F., Ordoñana, J.R., 2017. Age and gender effects on the prevalence of poor sleep quality in the adult population. Gac Sanit. 31(1):18-22. doi: 10.1016/j.gaceta.2016.05.013.

Mahoney, M.M., 2010. Shift work, jet lag, and female reproduction. Int J Endocrinol. 2010:813764. doi: 10.1155/2010/813764.

Maire, M., Reichert, C.F., Gabel, V., Viola, A.U., Strobel, W., Krebs, J., Landolt, H.P., Bachmann, V., Cajochen, C., Schmidt, C., 2014. Sleep ability mediates individual differences in the vulnerability to sleep loss: Evidence from a PER3 polymorphism. Cortex 52, 47–59. https://doi.org/10.1016/j.cortex.2013.11.008

Mallampalli, M.P., Carter, C.L., 2014. Exploring Sex and Gender Differences in Sleep Health: A Society for Women's Health Research Report. J Womens Health (Larchmt). 23(7): 553–562. doi: 10.1089/jwh.2014.4816.

Marcheva, B., Ramsey, K.M., Buhr, E.D., Kobayashi, Y., Su, H., Ko, C.H., Ivanova, G., Omura, C., Mo, S., Martha, H., Lopez, J.P., Philipson, L.H., Bradfield, C.A., Seth, D., Jebailey, L., Wang, X., Takahashi, J.S., 2011. Disruption of the Clock Components CLOCK and BMAL1 Leads to Hypoinsulinemia and Diabetes. Nature 466, 627–631. https://doi.org/10.1038/nature09253.Disruption

Melhuish Beaupre, L., Brown, G.M., Kennedy, J.L., 2018. Circadian genes in major depressive disorder. World J Biol Psychiatry. 21(2):80-90. doi: 10.1080/15622975.2018.1500028

Mermet, J., Yeung, J., Naef, F., 2017. Systems chronobiology: Global analysis of gene regulation in a 24-hour periodic world. Cold Spring Harb Perspect Biol. 9(3):a028720. doi: 10.1101/cshperspect.a028720.

Micic, G., de Bruyn, A., Lovato, N., Wright, H., Gradisar, M., Ferguson, S., Burgess, H.J., Lack, L., 2013. The endogenous circadian temperature period length (tau) in delayed sleep phase disorder compared to good sleepers. J. Sleep Res. 22, 617–624. https://doi.org/10.1111/jsr.12072

Middelkoop, H. A., Smilde-van den Doel, D. A., Neven, A. K., Kamphuisen, H. A. & Springer, C. P., 1996. Subjective sleep characteristics of 1,485 males and females aged 50–93: Efects of sex and age, and factors related to self-evaluated quality of sleep. J. Gerontol. A Biol. Sci. Med. Sci. 51, M108–M115. https://doi.org/10.1093/gerona/51a.3.m108.

Mistlberger, R.E., Skene, D.J., 2004. Social influences on mammalian circadian rhythms: Animal and human studies. Biol Rev Camb Philos Soc. 79(3):533-56. doi: 10.1017/s1464793103006353.

Moore, R.Y., Lenn, N.J., 1972. A retinohypothalamic projection in the rat. J Comp Neurol. 146(1):1-14. doi: 10.1002/cne.901460102.

Mong, J.A., Cusmano, D.M., 2016. Sex differences in sleep: impact of biological sex and sex steroids. Philos Trans R Soc Lond B Biol Sci. 371(1688):20150110. doi: 10.1098/rstb.2015.0110.

Morin, L.P., 2013. Neuroanatomy of the extended circadian rhythm system. E Exp Neurol. 243:4-20. doi: 10.1016/j.expneurol.2012.06.026

Münch, M., Silva, E.J., Ronda, J.M., Czeisler, C.A., Duffy, J.F., 2010. EEG sleep spectra in older adults across all circadian phases during NREM sleep. Sleep 33, 389-401. https://doi.org/10.1093/sleep/33.3.389

Münch, M., Wirz-Justice, A., Brown, S.A., Kantermann, T., Martiny, K., Stefani, O., Vetter, C., Wright, K.P., Wulff, K. and Skene, D.J., 2020. The role of daylight for humans: gaps in current knowledge. Clocks & sleep, 2(1), pp.61-85.

Mure, L.S., Le, H.D., Benegiamo, G., Chang, M.W., Rios, L., Jillani, N., Ngotho, M., Kariuki, T., Dkhissi-Benyahya, O., Cooper, H.M., Panda, S., 2018. Diurnal transcriptome atlas of a primate across major neural and peripheral tissues. Science. 359(6381):eaao0318. doi: 10.1126/science.aao0318

Myung, J., Schmal, C., Hong, S., Tsukizawa, Y., Rose, P., Zhang, Y., Holtzman, M.J., De Schutter, E., Herzel, H., Bordyugov, G., Takumi, T., 2018. The choroid plexus is an important circadian clock component. Nat Commun. 9(1):1062. doi: 10.1038/s41467-018-03507-2

Najjar, R.P., Zeitzer, J.M., 2016. Temporal integration of light flashes by the human circadian system. J. Clin. Invest. 126, 938–947. https://doi.org/10.1172/JCI82306

Nakao, M., McGinty, D., Szymusiak, R., Yamamoto, M., 1995a. A thermoregulatory model of sleep control. Jpn J Physiol. 45(2):291-309. doi: 10.2170/jjphysiol.45.291

Nakao, M., McGinty, D., Szymuziak, R., Yamamoto, M., 1995b. Dynamical Features of Thermoregulatory Model of Sleep Control. Jpn J Physiol. 1995;45(2):311-26. doi: 10.2170/jjphysiol.45.311.

Nasir-Ahmad, S., Lee, S.C.S., Martin, P.R., Grünert, U., 2019. Melanopsin-expressing ganglion cells in human retina: Morphology, distribution, and synaptic connections. J. Comp. Neurol. 527, 312–327. https://doi.org/10.1002/cne.24176

Nedergaard, M., 2013. Neuroscience. Garbage truck of the brain. Science. 340(6140):1529-30. doi: 10.1126/science.1240514.

Nesbitt, A.D., Dijk, D.-J., 2014. Out of synch with society: an update on delayed sleep phase disorder. Curr Opin Pulm Med. 20(6):581-7. doi: 10.1097/MCP.0000000000000095.

Nicholas, B., Rudrasingham, V., Nash, S., Kirov, G., Owen, M. J., Wimpory, D. C., 2007. Association of Per1 and Npas2 with autistic disorder: support for the clock genes/social timing hypothesis. Molecular psychiatry, 12(6), 581-592.

Nicolaides, N.C., Chrousos, G.P., 2020. Sex differences in circadian endocrine rhythms: Clinical implications. Eur J Neurosci. 2020 Jul;52(1):2575-2585. doi: 10.1111/ejn.14692.

Obayashi, K., Saeki, K., Tone, N., Iwamoto, J., Miyata, K., Ikada, Y., Kurumatani, N., 2015. Lower melatonin secretion in older females: gender differences independent of light exposure profiles. J Epidemiol. 25(1):38-43. doi: 10.2188/jea.JE20140035.

O'Connor, P.J., Morgan, W.P., Koltyn, K.F., Raglin, J.S., Turner, J.G., Kalin, N.H., 1991. Air travel across four time zones in college swimmers. J Appl Physiol (1985). 70(2):756-63. doi: 10.1152/jappl.1991.70.2.756.

Ohayon, M.M., Carskadon, M.A., Guilleminault, C., Vitiello, M.V., 2004. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. Sleep 27, 1255–1273. https://doi.org/10.1093/sleep/27.7.1255.

Olcese, J.M., 2020. Melatonin and Female Reproduction: An Expanding Universe. Front Endocrinol (Lausanne). 11: 85. doi: 10.3389/fendo.2020.00085.

Panda, S., 2016. Circadian physiology of metabolism. Science. 354(6315):1008-1015. doi: 10.1126/science.aah4967

Pandi-Perumal, S.R., Smits, M., Spence, D.W., Srinivasan, V., Cardinali, D.P., Lowe, A.D., Kayumov, L., 2007. Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. Prog Neuropsychopharmacol Biol Psychiatry. 31(1):1-11. doi: 10.1016/j.pnpbp.2006.06.020.

Pandi-Perumal, S.R., Srinivasan, V., Maestroni, G.J.M., Cardinali, D.P., Poeggeler, B., Hardeland, R., 2006. Melatonin: Nature’s most versatile biological signal? FEBS J. 273(13):2813-38. doi: 10.1111/j.1742-4658.2006.05322.x

Pandi-Perumal, S.R., Trakht, I., Spence, D.W., Srinivasan, V., Dagan, Y., Cardinali, D.P., 2008. The roles of melatonin and light in the pathophysiology and treatment of circadian

rhythm sleep disorders. Nat Clin Pract Neurol. 4(8):436-47. doi: 10.1038/ncpneuro0847.

Patke, A., Murphy, P.J., Onat, O.E., Krieger, A.C., Özçelik, T., Campbell, S.S., Young, M.W., 2017. Mutation of the Human Circadian Clock Gene CRY1 in Familial Delayed Sleep Phase Disorder. Cell 169, 203-215.e13. https://doi.org/10.1016/j.cell.2017.03.027

Phillips, A.J.K., Czeisler, C.A., Klerman, E.B., 2011. Revisiting spontaneous internal desynchrony using a quantitative model of sleep physiology. J. Biol. Rhythms 26, 441–453. doi: 10.1177/0748730411414163. https://doi.org/10.1177/0748730411414163

Phillips, A.J.K., Vidafar, P., Burns, A.C., McGlashan, E.M., Anderson, C., Rajaratnam, S.M., Lockley, S.W., Cain, S.W., 2019. High sensitivity and interindividual variability in the response of the human circadian system to evening light. Proc Natl Acad Sci U S A. 2019 Jun 11;116(24):12019-12024. doi: 10.1073/pnas.1901824116.

Pontes, A.L.B. de, Engelberth, R.C.G.J., Nascimento, E. da S., Cavalcante, J.C., Costa, M.S.M. de O., Pinato, L., Toledo, C.A.B. de, Cavalcante, J. de S., 2010. Serotonin and circadian rhythms. Psychol. Neurosci. 3, 217–228. https://doi.org/10.3922/j.psns.2010.2.011

Putilov, A.A., Russkikh, G.S., Danilenko, K. V., 1999. Phase of melatonin rhythm in winter depression, in: Advances in Experimental Medicine and Biology. Adv Exp Med Biol. 460:441-58. doi: 10.1007/0-306-46814-x_53

Ralph, M.R., Foster, R.G., Davis, F.C., Menaker, M., 1990. Transplanted suprachiasmatic nucleus determines circadian period. Science. 247(4945):975-8. doi: 10.1126/science.2305266

Rechtschaffen, A., Hauri, P., Zeitlin, M., 1966. Auditory Awakening Thresholds in REM and NREM Sleep Stages. Percept Mot Skills. 22(3):927-42. doi: 10.2466/pms.1966.22.3.927

Reiter, R.J., Tan, D.X., Kim, S.J., Cruz, M.H.C., 2014. Delivery of pineal melatonin to the brain and SCN: role of canaliculi, cerebrospinal fluid, tanycytes and Virchow–Robin perivascular spaces. Brain Struct Funct. 219(6):1873-87. doi: 10.1007/s00429-014-0719-7

Reiter, R.J., Tan, D.X., Korkmaz, A., Ma, S., 2012. Obesity and metabolic syndrome: Association with chronodisruption, sleep

deprivation, and melatonin suppression. Ann Med. 44(6):564-77. doi: 10.3109/07853890.2011.586365

Reyner, L.A., Horne, J.A., Reyner, A., 1995. Gender- and age-related differences in sleep determined by home-recorded sleep logs and actimetry from 400 adults. Sleep 18, 127–134. PMID: 7792492

Reynolds 3rd, C.F., O'Hara, R., 2013. DSM-5 Sleep-Wake Disorders Classification: Overview for Use in Clinical Practice. Am. J. Psychiatry 170, 1099–1101. https://doi.org/10.1176/appi.ajp.2013.13010058

Richter, C.P., 1960. Biological clocks in medicine and psychiatry: Shock-phase hypothesis. Proc Natl Acad Sci U S A. 46(11):1506-30. doi: 10.1073/pnas.46.11.1506

Richter, C.P., 1965. Biological clocks in medicine and psychiatry. Charles T. Thomas, Springfield, Illinois.p. 109. ASIN: B001STOOKY.

Richter, C.P., 1967. Sleep and activity: Their relation to the 24-hour clock. Res Publ Assoc Res Nerv Ment Dis. 45:8-29. PMID: 6083201.

Rijo-Ferreira, F., Takahashi, J.S., 2019. Genomics of circadian rhythms in health and disease. Genome Med 11, 82. https://doi.org/10.1186/s13073-019-0704-0.

Roybal, K., Theobold, D., Graham, A., DiNieri, J.A., Russo, S.J., Krishnan, V., Chakravarty, S., Peevey, J., Oehrlein, N., Birnbaum, S., Vitaterna, M.H., Orsulak, P., Takahashi, J.S., Nestler, E.J., Carlezon, W.A., McClung, C.A., 2007. Mania-like behavior induced by disruption of CLOCK. Proc. Natl. Acad. Sci. U. S. A. 104, 6406–6411. https://doi.org/10.1073/pnas.0609625104

Rusak, B. Chronobiology and mood disorders: background and introduction. J Psychiatry Neurosci. 2000 Nov;25(5):443-5. PMCID: PMC1408024.

Rusterholz, T., Tarokh, L., Van Dongen, H.P.A., Achermann, P., 2017. Interindividual differences in the dynamics of the homeostatic process are trait-like and distinct for sleep versus wakefulness. J. Sleep Res. 26, 171–178. https://doi.org/10.1111/jsr.12483

Sack, R.L., Brandes, R.W., Kendall, A.R., Lewy, A.J., 2000. Entrainment of free-running circadian rhythms by melatonin in

blind people. N Engl J Med. 343(15):1070-7. doi: 10.1056/NEJM200010123431503

Sadun, A.A., Schaechter, J.D., Smith, L.E.H., 1984. A retinohypothalamic pathway in man: Light mediation of circadian rhythms. Brain Res. 302, 371–377. https://doi.org/10.1016/0006-8993(84)90252-X

Salgado-Delgado, R., Tapia Osorio, A., Saderi, N., Escobar, C., 2011. Disruption of circadian rhythms: a crucial factor in the etiology of depression. Depress Res Treat. 2011:839743. doi: 10.1155/2011/839743

Santhi, N., Lazar, A.S., McCabe, P.J., Lo, J.C., Groeger, J.A., 2016. Sex differences in the circadian regulation of sleep and waking cognition in humans. Proc Natl Acad Sci U S A. 113(19):E2730-9. doi: 10.1073/pnas.1521637113.

Saper, C.B., 2013. The neurobiology of sleep. Continuum (Minneap Minn). 19(1 Sleep Disorders):19-31. doi: 10.1212/01.CON.0000427215.07715.73

Saper, C.B., Fuller, P.M., 2017. Wake–sleep circuitry: an overview. Curr Opin Neurobiol. 44:186-192. doi: 10.1016/j.conb.2017.03.021

Saper, C.B., Scammell, T.E., Lu, J., 2005. Hypothalamic regulation of sleep and circadian rhythms. Nature. 437(7063):1257-63. doi: 10.1038/nature04284.

Sateia, M.J., 2014. International classification of sleep disorders-third edition highlights and modifications. Chest 146, 1387–1394. https://doi.org/10.1378/chest.14-0970

Schulz, P., 2007. Biological clocks and the practice of psychiatry. Dialogues Clin. Neurosci. 9, 237–255. doi: 10.31887/DCNS.2007.9.3/pschulz

Serretti, A., Cusin, C., Benedetti, F., Mandelli, L., Pirovano, A., Zanardi, R., Colombo, C., Smeraldi, E., 2005. Insomnia improvement during antidepressant treatment and CLOCK gene polymorphism. Am. J. Med. Genet. B. Neuropsychiatr. Genet. 137B:36-39.

Sherin, J.E., Elmquist, J.K., Torrealba, F., Saper, C.B., 1998. Innervation of histaminergic tuberomammillary neurons by GABAergic and galaninergic neurons in the ventrolateral preoptic nucleus of the rat. J. Neurosci. 18, 4705–21. doi: 10.1523/JNEUROSCI.18-12-04705.1998

Shi, S.Q., White, M.J., Borsetti, H.M., Pendergast, J.S., Hida, A., Ciarleglio, C.M., De Verteuil, P.A., Cadar, A.G., Cala, C., McMahon, D.G. and Shelton, R.C., 2016. Molecular analyses of circadian gene variants reveal sex-dependent links between depression and clocks. Translational psychiatry, 6(3), pp.e748-e748.

Shiromani, P.J., Peever, J.H., 2017. New neuroscience tools that are identifying the sleep-wake circuit. Sleep. 2017 40(4):zsx032. doi: 10.1093/sleep/zsx032

Shukla, M., Govitrapong, P., Boontem, P., Reiter, R.J., Satayavivad, J., 2017. Mechanisms of Melatonin in Alleviating Alzheimer's Disease. Curr Neuropharmacol. 15(7):1010-1031. doi: 10.2174/1570159X15666170313123454

Skeldon, A.C., Dijk, D.J., Derks, G., 2014. Mathematical models for sleep-wake dynamics: Comparison of the two-process model and a mutual inhibition neuronal model. PLoS One. 9(8): e103877. doi: 10.1371/journal.pone.0103877

Srinivasan, V., Pandi-Perumal, S.R., Trahkt, I., Spence, D.W., Poeggeler, B., Hardeland, R., Cardinali, D.P., 2009. Melatonin and melatonergic drugs on sleep: Possible mechanisms of action. Int J Neurosci. 119(6):821-46. doi: 10.1080/00207450802328607

Stachurska, A., Sarna, T., 2019. Regulation of Melanopsin Signaling: Key Interactions of the Nonvisual Photopigment. Photochem Photobiol. 95(1):83-94. doi: 10.1111/php.12995

Stephan, F.K., Zucker, I., 1972. Circadian Rhythms in Drinking Behavior and Locomotor Activity of Rats Are Eliminated by Hypothalamic Lesions. Proc Natl Acad Sci U S A. 169(6):1583-6. doi: 10.1073/pnas.69.6.1583

Stothard, E.R., McHill, A.W., Depner, C.M., Birks, B.R., Moehlman, T.M., Ritchie, H.K., Guzzetti, J.R., Chinoy, E.D., LeBourgeois, M.K., Axelsson, J., Wright, K.P., 2017. Circadian Entrainment to the Natural Light-Dark Cycle across Seasons and the Weekend. Curr. Biol. 27(4):508-513. https://doi.org/10.1016/j.cub.2016.12.041

Stranges, S., Tigbe, W., Gómez-Olivé, F.X., Thorogood, M., Kandala, N.B., 2012. Sleep problems: an emerging global epidemic? Findings from the INDEPTH WHO-SAGE study among more than 40,000 older adults from 8 countries across Africa and Asia. Sleep. 35(8):1173-81. doi: 10.5665/sleep.2012.

Sukumaran, S., Almon, R.R., DuBois, D.C., Jusko, W.J., 2010. Circadian rhythms in gene expression: Relationship to physiology, disease, drug disposition and drug action. Adv Drug Deliv Rev. 62(9-10):904-17. doi: 10.1016/j.addr.2010.05.009.

Suntsova, N., Dergacheva, O., 2003. Dynamics of neuron activity in the lateral preoptic area of the hypothalamus during the sleep-waking cycle. Neurosci Behav Physiol. 33(7):651-8. doi: 10.1023/a:1024452522100

Suntsova, N., Szymusiak, R., Alam, M.N., Guzman-Marin, R., McGinty, D., 2002. Sleep-waking discharge patterns of median preoptic nucleus neurons in rats. J. Physiol. 543, 665–677. https://doi.org/10.1113/jphysiol.2002.023085

Suzuki, M., Furihata, R., Konno, C. Konno, M., kaneita, Y., Ohida T., Gon, Y., Uchiyama, M., 2019. Sleep disturbance is associated with not only shorter sleep duration, but also longer time in bed: a Japanese general population survey. Sleep Biol. Rhythms 17, 407–415. https://doi.org/10.1007/s41105-019-00228-x.

Takahashi, J.S., 2017. Transcriptional architecture of the mammalian circadian clock. Nat Rev Genet. 18(3):164-179. doi: 10.1038/nrg.2016.150

Takao, T., Tachikawa, H., Kawanishi, Y., Mizukami, K. and Asada, T., 2007. CLOCK gene T3111C polymorphism is associated with Japanese schizophrenics: a preliminary study. Eur Neuropsychopharmacol. 17(4):273-6. doi: 10.1016/j.euroneuro.2006.09.002.

Tang, J., Liao, Y., Kelly, B.C., Xie, L., Xiang, Y.T., Qi, C., Pan, C., Hao, W., Liu, T., Zhang, F., Chen, X., 2017. Gender and Regional Differences in Sleep Quality and Insomnia: A General Population-based Study in Hunan Province of China. Scientific Reports 7:43690, DOI: 10.1038/srep43690.

Taniyama, Y., Yamauchi, T., Takeuchi, S., Kuroda, Y., 2015. PER1 polymorphism associated with shift work disorder. Sleep Biol. Rhythms. 13:342–347. https://doi.org/10.1111/sbr.12123

Toh, K.L., Jones, C.R., He, Y., Eide, E.J., Hinz, W.A., Virshup, D.M., Ptacek, L.J., Fu, Y.-H.H., Ptácek, L.J., Fu, Y.-H.H., Ptacek, L.J., Fu, Y.-H.H., Ptácek, L.J., Fu, Y.-H.H., 2001. An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. Science (80-.). 291, 1040–1043.

https://doi.org/10.1126/science.1057499

Tong, Q., Ye, C., Jones, J., Elmquist, J., Lowell, B., 2008. Synaptic release of GABA by AgRP neurons is required for normal regulation of energy balance. Nat. Neurosci. 11, 99-.100. https://doi.org/10.1038/nn.2167,

Tong, Q., Ye, C.P., McCrimmon, R.J., Dhillon, H., Choi, B., Kramer, M.D., Yu, J., Yang, Z., Christiansen, L.M., Lee, C.E., Choi, C.S., Zigman, J.M., Shulman, G.I., Sherwin, R.S., Elmquist, J.K., Lowell, B.B., 2007. Synaptic Glutamate Release by Ventromedial Hypothalamic Neurons Is Part of the Neurocircuitry that Prevents Hypoglycemia. Cell Metab. 5, 383–393. https://doi.org/10.1016/j.cmet.2007.04.001

Traynor, K., 2014. Tasimelteon approved for circadian disorder in blind adults. Am. J. Heal. Pharm. 71, 350–350. https://doi.org/10.2146/news140017

Tsai, L.L., Li, S.P., 2004. Sleep patterns in college students: gender and grade differences. J Psychosom Res. 56(2):231-7. doi: 10.1016/S0022-3999(03)00507-5.

Uhlig, B.L., Sand, T., Odegård, S.S, Hagen, K., 2014. Prevalence and associated factors of DSM-V insomnia in Norway: the Nord-Trøndelag Health Study (HUNT 3). Sleep Med. 15:708–13. doi: 10.1016/j.sleep.2014.01.018.

Van Der Meijden, W.P., Van Someren, J.L., Te Lindert, B.H.W., Bruijel, J., Van Oosterhout, F., Coppens, J.E., Kalsbeek, A., Cajochen, C., Bourgin, P., Van Someren, E.J.W., 2016. Individual differences in sleep timing relate to Melanopsin-based phototransduction in healthy adolescents and young adults. Sleep 39, 1305–1310. https://doi.org/10.5665/sleep.5858

Von Economo, C., 1930. Sleep as a problem of localization. Journal of Nervous and Mental Disease, 71, 249–259. https://doi.org/10.1097/00005053-193003000-00007.

Waterhouse, J., Drust, B., Weinert, D., Edwards, B., Gregson, W., Atkinson, G., Kao, S., Aizawa, S., Reilly, T., 2005. The circadian rhythm of core temperature: origin and some implications for exercise performance. Chronobiol Int. 22(2):207-25. doi: 10.1081/cbi-200053477.

Watson, L.A., Phillips, A.J.K., Hosken, I.T., McGlashan, E.M., Anderson, C., Lack, L.C., Lockley, S.W., Rajaratnam, S.M.W., Cain, S.W., 2018. Increased sensitivity of the circadian

system to light in delayed sleep-wake phase disorder. J. Physiol. 596, 6249–6261. https://doi.org/10.1113/JP275917

Webb, W.B., 1994. Sleep as a biological rhythm: a historical review. Sleep 17, 188–194. https://doi.org/10.1093/sleep/17.2.188

Wirz-Justice, A., 2007. Chronobiology and psychiatry. Sleep Med. Rev. 11, 423–427. https://doi.org/10.1016/j.smrv.2007.08.003

Wirz-Justice, A., 2006. Biological rhythm disturbances in mood disorders. Int. Clin. Psychopharmacol. 21 Suppl 1, S11–S15. doi: 10.1097/01.yic.0000195660.37267.cf

Wirz-Justice, A., 2003. Chronobiology and mood disorders. Dialogues Clin. Neurosci. https://doi.org/10.5455/cap.20110317

Wright Jr, K. P., McHill, A. W., Birks, B. R., Griffin, B. R., Rusterholz, T., & Chinoy, E. D. (2013). Entrainment of the human circadian clock to the natural light-dark cycle. Current Biology, 23(16), 1554-1558.

Wulff, K., Gatti, S., Wettstein, J.G., Foster, R.G., 2010. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat. Rev. 11, 589–599. https://doi.org/10.1038/nrn2868; 10.1038/nrn2868

Xu, X., Breen, G., Chen, C.K., Huang, Y.S., Wu, Y.Y., Asherson, P., 2010. Association study between a polymorphism at the 3'-untranslated region of CLOCK gene and attention deficit hyperactivity disorder. Behav. Brain Funct. 12:6:48.

Yamashita, T., Yamanaka, A., 2017. Lateral hypothalamic circuits for sleep-wake control. Curr Opin Neurobiol. 44:94-100. doi: 10.1016/j.conb.2017.03.020

Yang, Z., Matsumoto, A., Nakayama, K., Jimbo, E.F., Kojima, K., Nagata, K.I., Iwamoto, S., Yamagata, T., 2016. Circadian-relevant genes are highly polymorphic in autism spectrum disorder patients. Brain Dev. 38(1):91-9. doi: 10.1016/j.braindev.2015.04.006.

Youngstedt, S.D., Elliott, J.A., Kripke, D.F., 2019. Human circadian phase–response curves for exercise. J. Physiol. 597, 2253–2268. https://doi.org/10.1113/JP276943

Zaki, N.F.W., Spence, D.W., BaHammam, A.S., Pandi-Perumal, S.R., Cardinali, D.P., Brown, G.M., 2018. Chronobiological theories of mood disorder. Eur Arch Psychiatry Clin Neurosci.

i

268(2):107-118. https://doi.org/10.1007/s00406-017-0835-5

Zaki, N.F.W., Spence, D.W., Subramanian, P., Bharti, V.K., Karthikeyan, R., BaHammam, A.S., Pandi-Perumal, S.R., 2020. Basic chronobiology: what do sleep physicians need to know? Sleep Sci. (Sao Paulo, Brazil) 13, 256–266. https://doi.org/10.5935/1984-0063.20200026

Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. J Physiol. 2000 Aug 1;526 Pt 3(Pt 3):695-702. doi: 10.1111/j.1469-7793.2000.00695.x. PMID: 10922269; PMCID: PMC2270041.

Zele, A.J., Feigl, B., Smith, S.S., Markwell, E.L., 2011. The circadian response of intrinsically photosensitive retinal ganglion cells. PLoS One. 6(3): e17860. doi: 10.1371/journal.pone.0017860

Zeng, L.N., Zong, Q.Q., Yang, Y., Zhang, L., Xiang, Y.F., Ng, C.H., Chen, L.G., Xiang, Y.T., 2020. Gender Difference in the Prevalence of Insomnia: A Meta-Analysis of Observational Studies. Front Psychiatry. 11: 577429. doi: 10.3389/fpsyt.2020.577429.

Zeppenfeld, D.M., Simon, M., Haswell, J.D., D'Abreo, D., Murchison, C., Quinn, J.F., Grafe, M.R., Woltjer, R.L., Kaye, J., Iliff, J.J., 2017. Association of perivascular localization of aquaporin-4 with cognition and Alzheimer disease in aging brains. JAMA Neurol. 74, 91–99. https://doi.org/10.1001/jamaneurol.2016.4370

Zhang, B., Wing, Y.K., 2006. Sex differences in insomnia: a meta-analysis. Sleep. 29:85–93. doi: 10.1093/sleep/29.1.85.

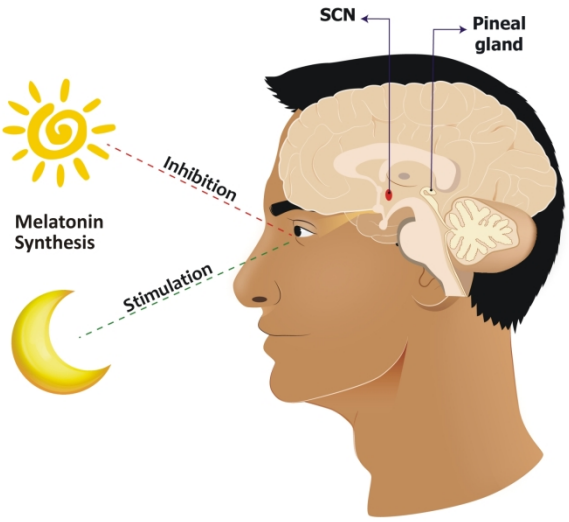
Zhang, J., Liao, G., Liu, C., Sun, L., Liu, Y., Wang, Y., Jiang, Z. and Wang, Z., 2011. The association of CLOCK gene T3111C polymorphism and hPER3 gene 54-nucleotide repeat polymorphism with Chinese Han people schizophrenics. Mol Biol Rep. 38(1):349-54. doi: 10.1007/s11033-010-0114-2.

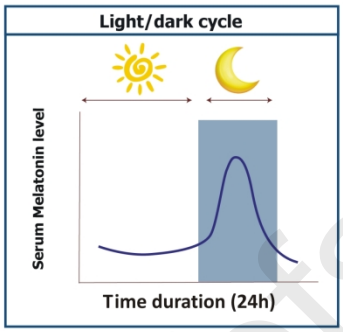
Zhang, L., Hirano, A., Hsu, P.K., Jones, C.R., Sakai, N., Okuro, M., McMahon, T., Yamazaki, M., Xu, Y., Saigoh, N., Saigoh, K., Lin, S.T., Kaasik, K., Nishino, S., Ptáček, L.J., Fu, Y.H., 2016. A PERIOD3 variant causes a circadian phenotype and is associated with a seasonal mood trait. Proc. Natl. Acad. Sci. U. S. A. 113, E1536–E1544. https://doi.org/10.1073/pnas.1600039113

Zhang, S.L., Yue, Z., Arnold, D.M., Artiushin, G., Sehgal, A., 2018. A Circadian Clock in the Blood-Brain Barrier Regulates Xenobiotic Efflux. Cell 173, 130-139.e10. https://doi.org/10.1016/j.cell.2018.02.017

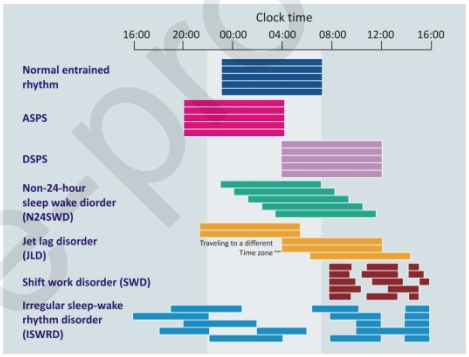
Zhu, J.L., Hjollund, N.H., Olsen, J., 2004. Shift work, duration of pregnancy, and birth weight: the National Birth Cohort in Denmark. Am J Obstet Gynecol 191: 285–291. doi: 10.1016/j.ajog.2003.12.002.

Zisapel, N., 2018. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. Br J Pharmacol. 175(16):3190-3199. doi: 10.1111/bph.14116





Sleep regulation



AANAT & HIOMT - Light regulation of two key enzymes involved in the biosynthetic pathway of melatonin

Room Light (< 200 lux)
Constant light (< 3 lux)
Light at Night
Light pollution

Suppresses melatonin → Sleep disturbances

AANAT - Aralkylamine N-acetyltransferase
HIOMT - Hydroxyindole-O-methyl transferase

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Figure 1.

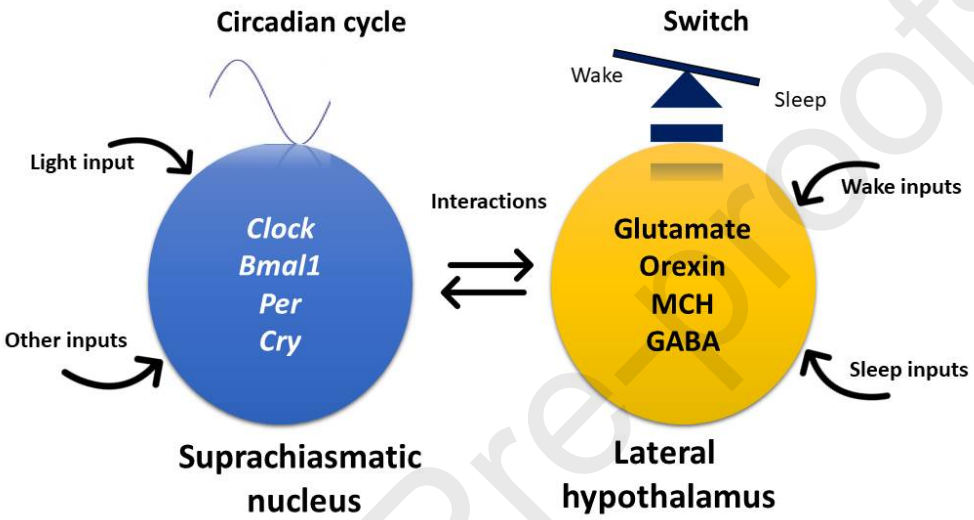


Figure 2.

Legends for the figures

Figure 1. a) Depicts the circadian rhythm of melatonin secretion and its involvement in sleep regulation. Figure b & c addresses the role of light on pineal melatonin synthesis, suppression, and subsequent sleep disruption. Generally, indoor room light (<500 lx) has been proven in investigations to generate substantial melatonin suppression and phase shift responses. Again the effect varies with experimental conditions, the nature of light, the time, the intensity, and the duration of administration. d) Shows various types of circadian rhythm sleep disorders..

Figure 2. Putative pathways linking the SCN and LHA in regulating sleep and wake timing in humans. The cyclic process in the SCN is cued by light signals from the melanopsin containing retinal cells travel via the RHT to the SCN. The 24 h cycle in SCN is based on the binding of CLOCK and BMAL1, which initiates the transcription and translation of PER and CRY, then the translated PER and CRY proteins repress CLOCK-BMAL1 function. This cycle interacts with the switch process in the lateral hypothalamus by an undefined pathway. The LHA of the diencephalon receives multiple external wake and sleep promoting neurons that act on OX neurons to promote waking and MCH neurons to promote REM sleep. Together with glutamate and GABA neurons, these are thought to control the switch from waking to sleep. This system provides inputs to the SCN that are yet to be defined. **Abbreviations used.** LHA, lateral hypothalamic area; MCH, melanin-concentrating hormone; OX, orexin/hypocretin; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus.

HIGHLIGHTS

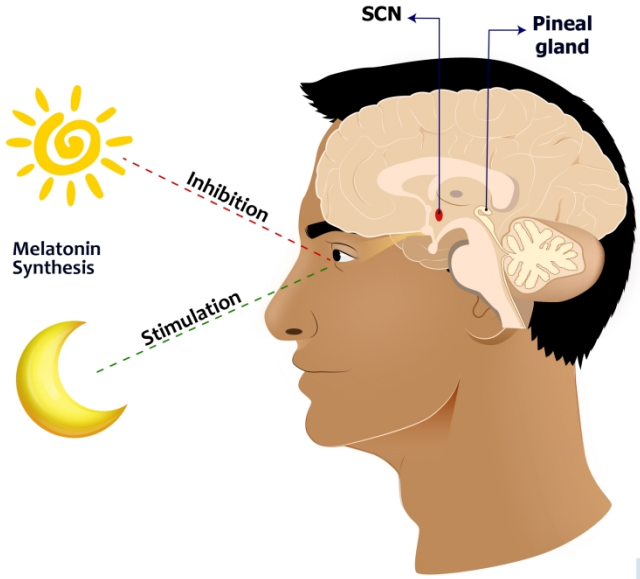
- In the brain, the organization of timing is essential for optimal brain physiology and function.

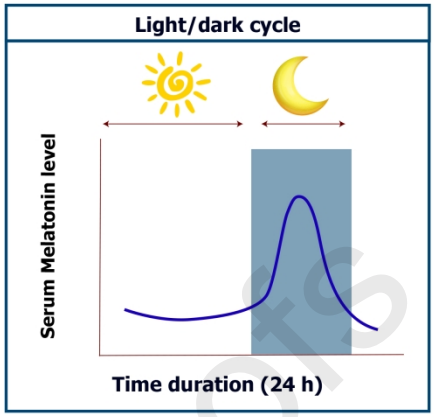
- Sleep and waking are meticulously timed and integrated with bodily functions

- For optimal functioning, the circadian clock and external stimuli must be properly aligned.

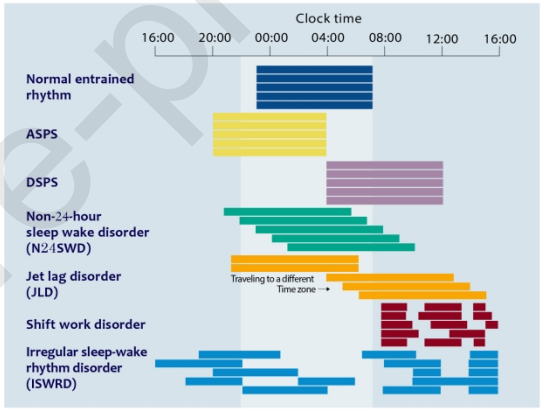
- In humans, failure results in circadian desynchrony and sleep/wake disturbances.

- The adaptive value of these processes to human health in the periodic environment is now formally recognized.





Sleep regulation



AANAT & HIOMT **- Light regulation of two key enzymes involved in the biosynthetic pathway of melatonin**

Room Light (< 200 lux)
Constant light (< 3 lux)
Light at Night
Light pollution

Suppresses melatonin → Sleep disturbances

AANAT - Aralkylamine N-acetyltransferase
HIOMT - Hydroxyindole-O-methyl transferase