Circadian and Light Effects on Human Sleepiness–Alertness

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Christian Cajochen, Sarah L. Chellappa and Christina Schmidt

2.1 Introduction

Most of our behavioral and physiological activities are modulated or regulated by endogenous clocks, chief among them the circadian (i.e., about a day) clock. Optimally located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus [1, 2], the circadian pacemaker in the SCN receives light information via the retinohypothalamic tract [3] directly from the retina's classical and nonclassical photoreceptors [4–6]. This light input is crucial, since circadian rhythms need to be entrained to the precise 24-h solar day in order to stay in sync with the daily light–dark cycle. Thus, most living organisms have adapted their temporal organization of behavior and physiology to optimally anticipate the 24-h light–dark cycle on earth. In fact, "light impacts on our circadian rhythms more powerful than any drug" as quoted by Charles Czeisler [7]. Thus, beyond vision, light has many physiological and neuropsychological repercussions on humans, which are referred as to nonvisual or nonimaging forming effects of light. Light attenuates the nocturnal release of the soporific hormone melatonin [8] even in some blind people [9], inhibits sleep-promoting GABA neurons in hypothalamic brain areas [10–12], and activates arousal-promoting orexin neurons in the hypothalamus [13]. In humans, light reduces sleepiness, increases alertness and cognitive performance, and also interferes with our sleep acutely [14–16] or via its circadian phase shifting properties [17].

C. Cajochen (✉) · C. Schmidt
Centre for Chronobiology, Psychiatric Hospital of the University of Basel, Wilhelm-Kleinstrasse 27, 4012, Basel, Switzerland
e-mail: Christian.Cajochen@upkbs.ch

S. L. Chellappa
Cyclotron Research Center, University of Liège, Liège, Belgium

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In this chapter, we address the importance of the circadian regulation of sleepiness–alertness and sleep and highlight the impact of light on sleep, neuroendocrine, alerting, and neurocognitive responses. Both the circadian and light effects on human sleepiness–alertness are far more complex and nuanced than initially thought. The aim is to increase our awareness of the importance of the circadian and acute effects of both natural and artificial light for human alertness–sleepiness regulation.

2.2 Definition and Measures of Alertness–Sleepiness

The terms sleepiness and alertness are being used interchangeably assuming that they describe the same phenomenon from different endpoints by either emphasizing sleep propensity or drowsiness (i.e., sleepiness) or wake propensity or attentiveness (i.e., alertness). There is no consensus among sleep experts as to which term best describes a status that alternates between a full asleep and full awake state in an alert–sleepy continuum. Some people describe it as drowsiness, tiredness, or simply fatigue, and to make things even more complicated different languages have smaller or richer facets of vocabularies for describing mental and/or physical fatigue. The precise meaning of the terms sleepiness, alertness, fatigue, or tiredness may also depend on the circumstances they are experienced or measured in (e.g., real life on shift work or at the wheel, or controlled conditions in a sleep laboratory).

In healthy people, alertness or sleepiness can be reliably measured by subjective rating scales (i.e., Karolinska Sleepiness Scale (KSS) or the Stanford Sleepiness Scale (SSS)). The Epworth Sleepiness Scale (ESS) is a subjective measure of sleep propensity in a variety of different situations [18]. In the laboratory, the gold standard for measuring sleep propensity represents the multiple sleep latency test (MSLT) under a particular test situation in a controlled sleep laboratory environment [19, 20]. Similarly, the maintenance of wakefulness test (MWT) [21] measures wake propensity under similar conditions as the MSLT. However, but both the MSLT and MWT do not measure sleepiness, in the sense that the KSS or the SSS measures it [22]. Thus, each of these tests which, assert to measure sleepiness by means of sleep propensity, actually measures different things is actually measuring something different [23], see also discussion in [24]. Thus, to objectively measure instantaneous sleepiness is difficult and makes the investigation of sleepiness related car accidents complex, since a gold standard, such as a "breathalyzer for sleep" does not exist [25]. From a neurophysiological perspective, there are promising variables, which reliably measure sleepiness in the field (e.g., at the wheel) and in the laboratory, particularly with respect to continuous sleepiness monitoring [26]. Reliable neurophysiological correlates of human alertness comprise electroencephalographic (EEG) frontal low-activity (1–7 Hz) and electrooculographic (EOG) slow rolling eye movements and eye blink rate [27], which closely correlate with the variability in the pupillary diameter [28]. The advantage of these measures is their high temporal resolution,

which allows detecting micro-sleeps or performance lapses in the range of seconds. A major disadvantage in their use in real-life settings (e.g., night shift work conditions in the field) is their interference-prone nature, particularly for the EEG and the need of interruption of ongoing activity for pupillometry techniques. However, recent advance has been made in developing devices specifically developed for objectively and continuously measuring sleepiness while driving a vehicle. One such method uses video camera images of the person's eye [29]. Another technique uses infrared reflectance oculography to measure the relative velocity and duration of eyelid movements during blinks and especially short-term variability of those characteristics, which allows to assess the risks of drowsiness while driving [30] and to tack changes in alertness and performance along the alert–drowsy continuum in a controlled laboratory setting [31].

2.3 Circadian Rhythms and Human Alertness/Sleepiness

The human 24-h sleep-wake cycle is rather monophasic roughly comprising 16 h of wakefulness followed by 8 h of sleep [32]. This is in sharp contrast to polyphasic sleep wake behaviors particularly in small animals, which is likely to reflect energetic constraints [33]. Despite the fact that humans can sustain relatively stable levels of wakefulness across 16 h, sleepiness–alertness levels during the waking day may fluctuate considerably, which depends on ongoing mental, physical activity, body posture, environmental influences (e.g., light, temperature, humidity, noise levels), prior sleep–wake history and individual factors such as age, sleep duration (i.e., long vs. short sleepers), as well as the individual chronotype (e.g., early vs. late chronotype). Besides all these important modulators of human alertness–sleepiness levels there is a major circadian control of them. It regulates alertness–sleepiness in a clock-like fashion despite, environmental and individual influences. From early on, alertness has been related to the time of day. Kleitman already noticed that the diurnal modulation of alertness shows a close temporal association with the diurnal rhythm of core body temperature with its maximum in the evening and nadir in the early morning [34]. More recently, it has been shown that the diurnal rhythm in human sleepiness is a quantifiable output from the circadian clock and closely follows the circadian core body temperature and melatonin rhythm [27, 35, 36]. This is best documented during nap protocols, when homeostatic sleep pressure is kept very low through multiple nap opportunities scheduled over the entire circadian cycle [Fig. 2.1, [36]]. The circadian sleepiness–alertness rhythm can be shifted by light—very much like the circadian rhythms of core body temperature and melatonin (Fig. 2.2). This is another strong indication that the circadian clock regulates human alertness–sleepiness levels. Furthermore, the contribution of circadian rhythmicity to alterations in subjective alertness has been quantified in constant routine and forced desynchrony protocols [35, 37, 38]. These protocols revealed that the contribution of the circadian pacemaker to variations of subjective alertness, performance, and sleep propensity was equal to the contribution of the sleep homeostat. The data further revealed that

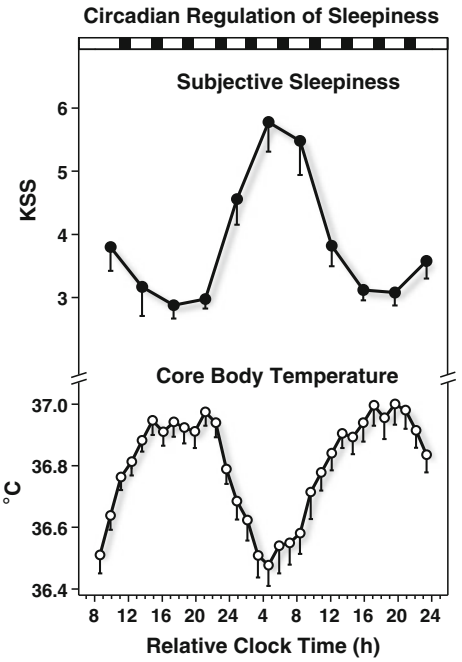

Fig. 2.1 Circadian regulation of sleepiness on the Karolinska Sleepiness Scale and core body temperature (CBT) across a 40-h nap protocol (low sleep pressure), with 10 alternating cycles of 150-min of scheduled wakefulness followed by 75-min of scheduled sleep. The *upper panel* indicates the timing of the naps (*black bars*) and scheduled episodes of wakefulness (*white bars*) respectively. Data were binned into 3.75 h time intervals for subjective sleepiness and into 1.25 h time intervals for CBT (mean values s.e.m., n = 10), and plotted against the midpoint of the time intervals. Relative clock time represents the average clock time at which the time intervals occurred. Adapted with permission from [36]

the detrimental effects of prior wakefulness on alertness were strongest close to the minimum of the endogenous core body temperature rhythm and that the circadian modulation of these variables increased with the amount of prior wakefulness [37–39]. The interpretation of these data led to the conclusion that stable and high levels of alertness can only be maintained when the phase relationship between the endogenous circadian timing system and the sleep/wake cycle is such that the circadian timing system opposes the wake-dependent deterioration of alertness and performance as conceptualized in the "opponent process" model [40, 41]. This is achieved most effectively when the waking day is initiated approximately 2 h after the endogenous circadian minimum of the core body temperature rhythm, which corresponds to approximately 3 h after the circadian maximum of the plasma melatonin rhythm. Thus, at least in humans, it seems that the circadian process represents a wake-promoting drive to balance the accumulating homeostatic drive for sleep during wakefulness [for a review see [42]].

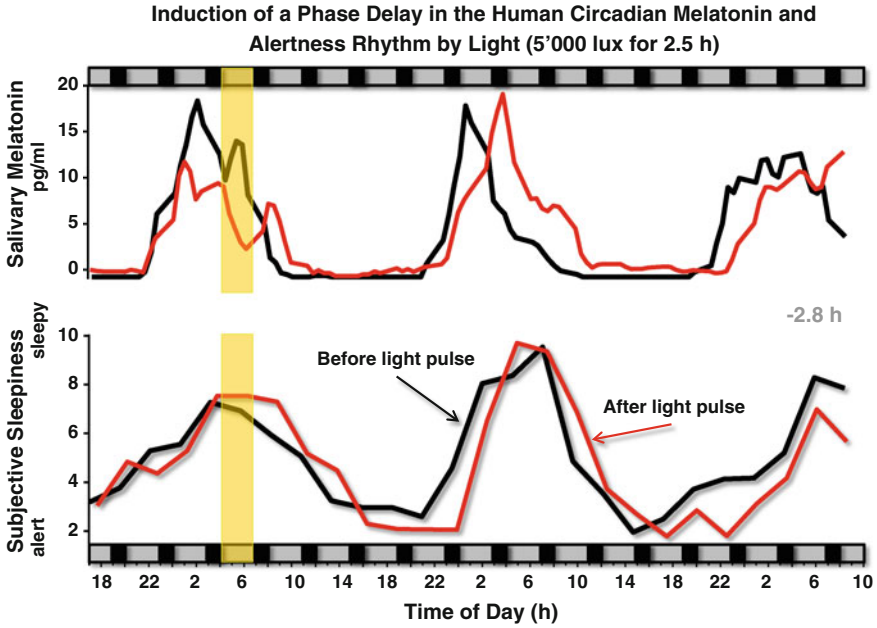

Fig. 2.2 Circadian regulation of sleepiness on the Karolinska Sleepiness Scale and salivary melatonin levels across a 64-h nap protocol (low sleep pressure), with 16 alternating cycles of 150-min of scheduled wakefulness followed by 75-min of scheduled sleep. Data of an individual study volunteer, who participated twice in the nap protocol, once without exposure to a light pulse and once exposed to a 2.5-h bright light pulse of 5000 lux during the second half of the first biological night. The light pulse delayed circadian phase of both the melatonin and sleepiness rhythm (ca. 2.8 h)

To allow for sleep inertia, a transitional state of lowered arousal experienced upon awaking from sleep, and additional process, process W, was introduced besides the circadian and the sleep homeostatic process [43]. Sleep inertia has been shown to exert a detrimental effect on cognition that last up to 4 h after awakening, depending on prior sleep duration [44]. Thus, it is closely related to circadian and homeostatic as well as thermoregulatory processes [45] and should not be underestimated in its impact on alertness.

The neuronal underpinnings of circadian and homeostatic sleep–wake regulation are described in detail in Chap. 4 for details on how sleep inertia impacts on cognition. Briefly, the key structure for the circadian regulation of the sleep–wake and many other behaviors is confined to the SCN in the anterior hypothalamus, optimally located above the optic chiasm in order to receive light from the eyes via the retinohypothalamic tract [3, 46]. The SCN regulates via paracrine secretion [47–49] and neural connections a variety of targets in the nearby hypothalamus and thalamus [50, 51]. The SCN itself has only a few monosynaptic outputs to sleep-regulatory centers such as the ventrolateral preoptic are (VLPO) and the lateral hypothalamus (LH) but not to arousal sites in the brainstem (for a review

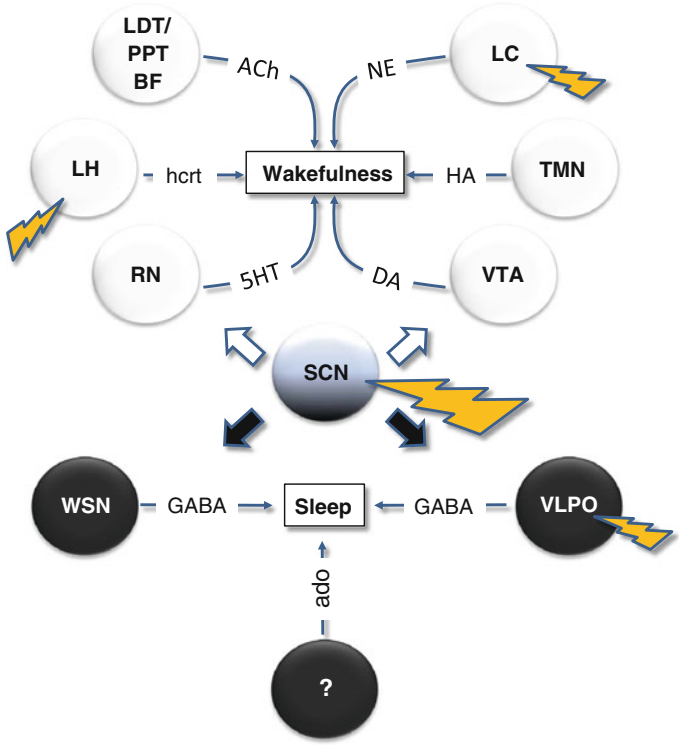

Fig. 2.3 Influence of neuromodulatory systems on wakefulness (*upper panel*) and sleep (*lower panel*). Each circle represents a different, anatomically distinct neurotransmitter system that promotes sleep or wake. Abbreviations: 5HT, serotonin; ACh, acetylcholine; ado, adenosine; BF, basal forebrain; DA, dopamine; GABA, gamma-aminobutyric acid; HA, histamine; hcrt, hypocretin; LC, locus coeruleus; LDT, laterodorsal tegmentum; LH, lateral hypothalamus; NE, norepinephrine; PPT, pendunculopontine tegmentum; RN, raphe nuclei; SCN, suprachiasmatic nucleus; TMN, tuberomamillary nucleus; VLPO, ventrolateral preoptic nucleus; VTA, ventral tegmental area; WSN, warm-sensitive neurons. Adapted with permission from [96]. The SCN is located in the middle as a major regulator of wake and sleep promoting neuromodulatory systems with direct and indirect multisynaptic networks, promoting wakefulness and sleep in a time-dependent manner. Brain areas for which light effects have been shown either in animal or humans fMRI studies are marked with *yellow* flashes

see [52]). Thus, the SCN regulates various sleep and wake promoting brain areas (see Fig. 2.3) via multisynaptic pathways with the subparaventricular zone (SPZ) as the most important relay structure [53]. The ventral SPZ drives the dorsomedial nucleus of the hypothalamus (DMH), which in turn is responsible for circadian rhythms of sleep-wake, locomotion, feeding, and corticosteroid secretion [53]. According to Saper et al. [54], these multiple relays in the hypothalamus probably integrate light-entrained circadian cues from the SCN with non-photic time cues from the environment in order to establish sleep–wake patterns that are most adaptive to an organism.

2.4 Light and Human Alertness/Sleepiness

The role of light as the major *Zeitgeber* (i.e., synchronizer) for human circadian entrainment has been firmly established over the past 40 years [55, 56]. From early on it was noticed that besides circadian photoentrainment, light also evokes non-circadian "masking" effects on behavior and physiology [57]. In human sleep and circadian research, the term "masking" is scarcely used and is often substituted by expressions such as "acute," "direct," or "non-circadian" effects of light when it comes to describe alerting properties of light. Badia et al. [58] were among the first to show that light can evoke acute alerting responses in humans, as indexed by elevated core body temperature levels and increased electroencephalographic (EEG) beta-activity during wakefulness along with increased alertness and performance levels during episodes of bright light exposure. Thereafter, non-circadian effects of light have been implemented in shift work environments where elevated light levels made night-shift workers more alert when they had their breaks in well-lit rooms [59]. Likewise, low-intensity, bright light and moderate blue light exposure promoted alertness during prolonged nighttime performance testing during a simulated night shift [60, 61]. These results were corroborated in non-shift workers during daytime such that a 4-week exposure to blue-enriched light during office hours improved well-being and alertness as well as sleep quality in comparison to a non-blue enriched light solution in the office [62]. Whether light changed circadian parameters such as the diurnal profile of melatonin secretion is not clear, since circadian profiles were not assessed in those studies. Thus, it could still be that light acted via its *Zeitgeber* property and in turn ameliorated the worker's well-being, alertness and sleep. Also considering the long-term application of light, the described effects were probably rather of *circadian* than *acute* nature. Thus, in our view, acute effects of light should only describe short-term effects, which minimally last for minutes and do not exceed 24 h (i.e. one circadian cycle maximally).

The discovery of the new photoreceptor system, the intrinsic photosensitive retinal ganglion cells (ipRGCs) containing the photopigment melanopsin [4–6], sensitive to 460-480 nm [5, 63–65], highlighted the importance of light's wavelength, blue light in particular, and has received substantial scientific interest [7] and media attention [66]. We and others performed multiple investigations on the acute effects of short-wavelength light and in *unison* found that light evokes alerting responses that crucially depend on time of day, light's intensity and wavelength composition, the duration of light exposure, and more recently, also on prior light–dark light history [14, 16, 60, 67–72]. If light is of sufficient intensity and applied during the biological night, when the circadian controlled release of melatonin is active, the alerting response typically occurs within 10 to 20 min after lights are on [70]. If the lights levels are lower and of monochromatic nature and as short as 50 s, no significant behavioral changes in alertness and cognitive performance were reported [for a review see [73]]. However, light evoked significant response in subcortical and cortical brain structures that were implicated in the task

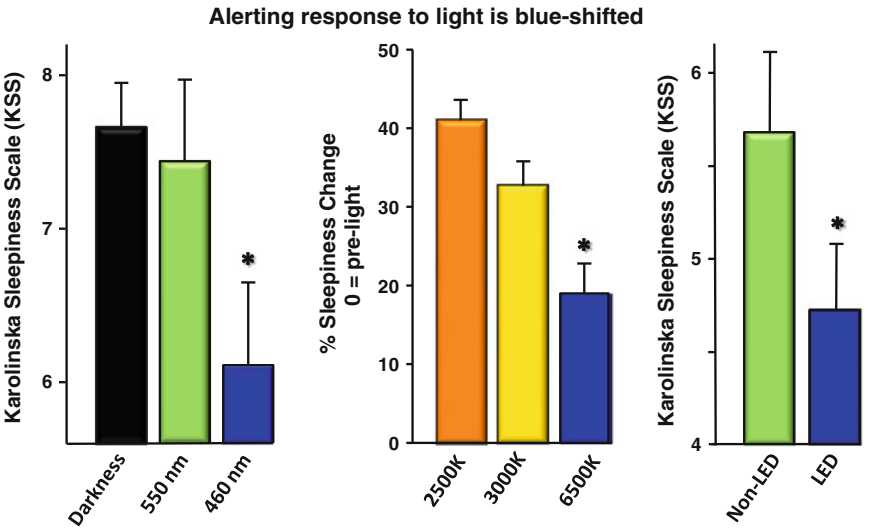

Fig. 2.4 Subjective sleepiness ratings on the KSS after different light exposures. *Left panel*, 2-h evening exposure to monochromatic light at 460 nm, 550 nm and no light (i.e., darkness) according to [14], *middle panel*, 2-h exposure to *blue-enriched light* (6,500 K), incandescent light at 3,000 K and *non-blue enriched light* at 2500 K according to [68], *right panel*, sleepiness levels during a simulated evening shift in front of a LED and non-LED computer screen according to [74]

the volunteers were performing during the functional imaging scans [73]. Thus, light may affect brain regions before any behavioral sign of this effect emerges and can be noticed. However, there is no need for light to be brighter than 500 lux and or to be exposed longer than 30 min to reliably measure nonvisual behavioral light effects in humans. We have current evidence that evening light levels as low as 40 lux evoke alerting responses and increase cognitive performance when blue-enriched or monochromatic at 460 nm in comparison to non-blue enriched and monochromatic light at 550 nm when the volunteers were dark-adapted before they were exposed to the corresponding light sources [Fig. 2.4, [14, 68]]. Interestingly, when performing two simulated evening shift in the laboratory one in front of a light emitting diodes (LED) computer screen and another one in front of a non- LED screen both with very similar light intensities, we still detected significant alerting effects of the LED screen and better performance in higher cognitive tasks compared to the non-LED condition [74]. Thus, it is rather the relative than the absolute light level in comparison to prior light exposure and/or the concurrent ambient light that determines the extent of nonvisual effects. In other words, it is the "extra light" that makes the difference—a fact, which has been recently proved in a controlled laboratory setting [72]. If humans are particularly sensitive to "extra light" coming from LED screens and other artificial light sources in the environment, this poses the question of whether the decreasing trend in habitual sleep duration and the concomitant prevalence of sleep disorders in our modern societies can also be attributed to too much "extra light," particularly in the late evening hours. Light in the evening can make

you acutely "bright," but has the potential to delay circadian rhythms and in turn negatively impacts on the circadian entrainment of sleep–wake and natural light–dark cycle, which can lead to daytime sleepiness and cognitive performance decrements—and thus makes you "dim" in the long run. There is an urgent need to further investigate on these potential interrelations, since there is epidemiological evidence that light at night (LAN) may negatively impact on human health [75]. Negative LAN effects played also a role in the WHO's decision to declare shift work, night shift work in particular, as potentially carcinogenic [76]. Besides LAN, interindividual differences in the nonvisual light response should be accounted for in further studies, since there is recent evidence that the alerting responses to light depend on a clock gene polymorphism [77], gender (own data in preparation), and age [78, 79] even when carefully controlled for prior light history, the amount of prior wakefulness and circadian phase.

The most obvious route for nonvisual light to reach the brain is through the eyes. Extra-retinal opsins (e.g., encephalopsin) exist in the human brain [80], but it is not clear whether they can function as photopigments in humans. Interestingly, there is new in vitro evidence that homologs of vertebrate Opn3 might function as photoreceptors in various tissues [81]. On the behavioral level, extraocular light perception has so far not being confirmed in humans [82–84]. Nonvisual light information is mainly deciphered by the ipRGCs via melanopsin, which integrate this information with signals from the classical photoreceptors to elicit nonvisual brain responses [for a review see [85, 86]]. The main target of nonvisual light is the SCN, and from there light information is spread via the SCN's multisynaptic output paths to many brain areas. In addition, light information is transmitted via different melanopsin receptors subtypes on different "non-SCN routes," directly to the VLPO, to control sleep, to the olivary pretectal nucleus (OPN) to control the pupillary light reflex, the lateral geniculate nucleus (LGN), and the superior colliculus (SC), implicated in a rudimentary, low-acuity visual function [87, 88]. Thus, nonvisual light is for much more than just circadian photoentrainment (for a review see [89]). For human alertness–sleepiness regulation, the direct route to the VLPO is potentially interesting, since light with appropriate wavelengths and intensity characteristic could be used to manipulate alertness and sleep without targeting the SCN. This would have the potential for a specific light regime for night shift conditions, with the purpose to optimize the worker's alertness levels without affecting their circadian timing system.

Besides sleep promoting areas, there is recent evidence that light can also impact on wake promoting brain areas in the lateral hypothalamus which contain hypocretin/orexin (Hcrt) neurons [13]. The effects of light on Hcrt neurons might be mediated directly by inputs from the retinohypothalamic tract [90] or indirectly by outputs from the SCN [91]. This interesting finding could also explain why light does not have alerting properties in narcoleptic patients as well as the weak diurnal rhythm in sleep propensity in these patients [92]. In human functional magnetic resonance imaging (fMRI) studies, blue light exposure enhanced activity in the posterior thalamus including the pulvinar nucleus, implicated in the regulation of visual attention and alertness, to green light [93]. Furthermore, light-induced

modulation of brain activity has also been shown for a location compatible with the locus coeruleus (LC) [93], which is an important noradrenergic wake-promoting brain region (Fig. 2.3), functionally connected with the SCN [94, 95]. This suggests that light may modulate activity in subcortical structures involved in alertness, and thereby promote cortical activity in networks involved in ongoing nonvisual cognitive processes [93].

2.5 Conclusion

The circadian timing system and light via the nonimage forming system contribute enormously to human alertness–sleepiness regulation. The discovery of the multifaceted neuronal underpinnings of the SCN's outputs as well as light's visual and nonvisual repercussions on the brain's sleep and wake-promoting regions is far more complex than initially thought. However, these discoveries along with the recent advances in solid-state LED technology, will help to design and implement potentially successful novel light devices and light exposure schedules at home and in the workplace environment.

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