Non-visual effects of light on human circadian physiology and neurobehavioral performance

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ABSTRACT

Light is of crucial importance for human circadian rhythms. In fact, light exposure allows for resetting individual biological rhythms to the 24-h day. Besides its synchronizing effects, light also acts on different behavioural and physiological variables. The overarching aim of this thesis was to investigate the effect of different light properties, such as intensity, wavelength, duration, timing and dynamics, on neurobehavioral performance and circadian physiology, and possible inter-individual differences.

In the first part, we investigated the effect of three morning light settings (dim light, DL < 8 lux; monochromatic blue light, mBL at 100 lux; and dawn simulation light, DsL increasing from 0 to 250 lux) in 17 young participants (20-35 years old), after two nights of 6-h sleep restriction, on alertness, well-being, melatonin and cortisol profiles and cognitive performance. We found that exposure to artificial morning DsL improved subjective perception of well-being and mood, as well as cognitive performance across the day compared to DL and mBL. Only morning mBL induced a phase advance of the circadian profile of melatonin, thus impacting on the circadian system.

In the second part, we compared the effect of three light settings (dim light, DL <8 lux; polychromatic white light, WL at 250 lux; and blue- enriched polychromatic white light, BL at 250 lux) on subjective sleepiness and physiological variables during a 40-h sleep deprivation protocol. Inter-individual differences were investigated with respect to (1) age, by enrolling a cohort of 26 young (20-35 years old) and 12 older participants (55-75 years old); and (2) genetic predisposition (polymorphism in clock gene *Period3*), by enrolling 8 young *PER3*$^{4/4}$ and 8 young *PER3*$^{5/5}$ participants. Accordingly, the age-related effects were such that exposure to BL and WL improved subjective sleepiness in both age groups, while melatonin suppression was only detectable in the young, with a more pronounced effect under BL, and not in the older. Only the blue-enriched light modified cortisol levels, with a decrease in the young and an increase in the older. Both lights had a contrary effect depending on the age of the participant in regard to skin temperature and motor activity. With respect to the genetic predisposition, exposure to BL and WL suppressed melatonin

in both groups, with a stronger effect under BL in the *PER3*$^{5/5}$. However, we showed a significant alerting response, a better well-being, and a decrease in cortisol levels only in the short allele carriers (*PER3*$^{4/4}$). In contrast, cognitive performance was decreased only in *PER3*$^{5/5}$ under WL.

In conclusion, depending on the purpose to use non-visual effects of light, either DsL or mDL can be used to improve subjective mood and cognitive performance or to shift internal rhythms, respectively. In a broader perspective, the use of moderately bright light in night work and shift work settings, where constant light levels are very common, may differ across shift workers given their age and their genetic predisposition.

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ABBREVIATIONS

BL: blue-enriched white light

CBT: core body temperature

DL: dim light

DLMO: dim light melatonin onset

DsL: dawn simulation light

EMR: electromagnetic radiation

HR: heart rate

ipRGC: intrinsically photosensitive retinal ganglion cells

LED: light emitting diode

LGN: lateral geniculate nucleus

mBL: monochromatic blue light

NIF: non-image forming or non-visual effect of light

PER3: *PERIOD3*

PRC: phase response curve

RHT: retinohypothalamic tract

SAD: seasonal affective disorder

SCN: suprachiasmatic nucleus

SD: sleep deprivation

SR: sleep restriction

VLPO: ventro-lateral preoptic nucleus

VNTR: variable number tandem repeat

WL: white light

I- Introduction

Light exerts a pivotal role in the entrainment of our 24-h circadian rhythms. Besides its “Zeitgeber” (“time giver”) function, non-visual light effects impact on behaviour and physiology, including hormonal secretion [4, 5], sleep-wake regulation (for a review, see [6]), cognition [7-9], and its underlying cerebral correlates [10]. These variables are regulated by a fine-tuned interaction of circadian and homeostatic processes that provide optimal alertness levels and cognitive performance during a normal waking day of approximately 16-h and a consolidated 8-h episode of nocturnal sleep (Cajochen et al., 2010). Therefore, for humans it is crucial to “catch” the light, through a non-visual neuronal pathway, mainly in the morning and in the evening in order to reset the human circadian rhythm to the 24-h earth rotation. However, the light can have different impacts according to its features, namely the intensity, timing, duration, wavelength and dynamic. While these non-visual or non-image forming light effect on sleepiness, well-being and melatonin suppression are well-described for light exposure in the late evening [8, 11, 12], daytime light exposure studies are less abundant [13-16] and extended light exposure studies are almost inexistent.

Since daytime light exposure can enhance alertness, in a first step, we wanted to test whether morning light exposure can counteract the detrimental effects of sleep restriction on alertness, mood, cognitive performance and physiological variables throughout the day in young people. In a next step, we investigated whether an extended light exposure can maintain similar effects than a morning light exposure, throughout the day or if these effects are “weakened” after reaching a “light threshold”.

Moreover, with healthy ageing, alterations in sleep and cognition as well as light perception occur. Sleep becomes typically more fragmented, there is less deep sleep (slow wave sleep), and impaired learning capacities with age [17]. So far, the desynchronization observed with ageing and its associated circadian changes is reported in some studies, but little is known on whether improving light perception (i.e. enhancing the zeitgeber stimulus) in the older population, could ameliorate physiological degradations associated with age. Thus, in a second step, we investigated the physiological and behavioural consequences of different light

exposure regimes on alertness and circadian rhythms in older compared to young volunteers.

Importantly, aging is not the only factor accounting for individual differences in the circadian system. Increasing evidence speaks for genetic factors underpinning both circadian and homeostatic sleep-dependent processes. According to previous reports, a variable number tandem repeat (VNTR) polymorphism of the clock gene *PERIOD3* (*PER3*) seems to be linked to sleep loss-related vulnerability on behavioural and physiological level in human [18-20]. Furthermore, it also has a differential impact on cognitive brain responses to light [21], on melatonin suppression and on the subjective alerting effect of light [22, 23]. Thus, in a third step, we investigated the impact of a prolonged light exposure on physiological and behavioural parameters in young individuals homozygous for the polymorphism in the clock gene *PERIOD3*.

Our data will provide insights on how to use different light modalities to improve individual's daily life.

II-Theoretical background

Rhythmicity is one of the fundamental properties of all organisms. Periodic variations, such as the alternation of day and night caused by the earth rotation, govern the functions of all living beings. Circadian rhythms (from the Latin circa, "about" and diem, "day") can be found in all metabolic, physiological and cognitive activities, which allow organisms to anticipate periodic environmental variations and thus ensure optimal functioning [24-27]. Circadian rhythms persist even when organisms are isolated from external time information (called “Zeitgeber”). They are defined by their period (about 24 hours), amplitude and phase relative to a reference time. Circadian rhythms can be measured in almost every physiological variable, whereby prominent examples are core body temperature rhythms, different hormonal rhythms, such as melatonin and cortisol, and sleep-wake rhythms. The light /dark cycle (LD) of 24 hours acts as “Zeitgeber” (i.e. time giver), to adjust circadian rhythms, which are not precisely 24-h, to the 24-h earth rotation [28, 29].

1/ The sleep-wake cycle

Sleep and wake are two different behavioural states characterised, respectively, by rest or activity, a decrease or increase of body movements, and unresponsiveness or responsiveness to external stimuli [30]. Sleep is regulated by two processes [31]: the circadian process (process C), which reflects the output of the self-sustained circadian clock; and the homeostatic process (process S), which represents the accumulation of sleep need and the propensity to initiate sleep. Inter-individual differences in sleep architecture could be explained by differences in these two processes [32].

1.1 Circadian process

Circadian rhythms are generated by a set of biological clocks within the whole body and organised in a hierarchical network comprising a central clock and multiple peripheral clocks [33, 34]. In mammals, the central clock is the suprachiasmatic nuclei (SCN) located in the anterior hypothalamus [35, 36]. Circadian rhythmicity

results from a complex molecular mechanism: at the cellular level, several transcriptional feedback loops, encoded by clock genes, involve clock proteins and need 24-h to ensure a complete cycle that includes transcription activation and deactivation [37, 38]. These feedback loops are also regulated by post-translational modifications and all these processes lead to a rhythmic expression of clock genes, which induce rhythmic expression of their target genes. Oscillations are transmitted to the SCN cells, thus resulting in a rhythmic neuronal activity enabling the synchronization of the whole body through specific effectors of the clock [37, 39, 40].
In humans, a classical marker (i.e. “hand of the clock”) of circadian rhythms is the neurohormone melatonin [41-43]. Melatonin is a hormone synthesized and rhythmically released by the pineal gland, where a nervous signal “converts” into a hormonal signal. This signal is released only during the night, thus representing an individual’s biological night. Melatonin secretion is also proportional to the duration of the nocturnal phase, such that it is longer in winter and shorter in summer, thus providing information on seasonality [44, 45]. Furthermore, melatonin does not critically depend on physiological parameters (e.g. stress), but mostly responds to light changes in the environment, giving a clear estimation of the period. Therefore, melatonin provides key information on the internal biological time during the 24h day and across seasons even though it has become difficult to adapt it at the modern human [46].

1.2. The sleep-wake homeostatic process

The accumulation of sleepiness during the day and the decrease in sleep propensity during the night represents the homeostatic process. It can be enhanced when sleep is curtailed or reduced when there is an excess of sleep. This is clearly demonstrated with sleep deprivation protocols that challenge homeostatic sleep mechanisms [47-50]. Furthermore, this high sleep pressure can be attenuated by short nap episodes [51, 52]. Sleep homeostasis is typically indexed by NREM slow-wave activity (SWA, 0.75- 4.5Hz) and waking theta activity (4.75-7Hz), which increases with extended time awake [53-55]. While the neuroanatomical and molecular substrates for the circadian process are well known, potential neuronal structures underscoring sleep homeostasis still remain to be clearly established.

1.3. Interaction of the two processes

Despite the controversy on whether it is the circadian or the homeostatic process that underpins sleep, there is large evidence for a crosstalk between these two systems for sleep/wake regulation [56]. For instance, inter-individual differences in sleep-wake timing and diurnal preference may not only reflect changes in the circadian process, but can also reflect a faster build-up of homeostatic sleep pressure during wakefulness and a faster dissipation during sleep [57]. The homeostatic sleep drive accumulates throughout the day and exponentially dissipates during sleep. The circadian system would then oppose the increasing homeostatic drive for sleep close to the end of the habitual wake day, by promoting an "arousal signal". Conversely, during the end of the sleep episode, when sleep pressure is greatly decreased, the circadian system would promote a "sleep signal" to ensure a longer sleep bout [31, 58].

These two processes not only impact on sleep regulation, but also on cognitive performance and mood [59, 60]. Neurobehavioral performance is typically impaired after the core body temperature nadir, postulated to be near regular wake-time. The opposite is true when sustained attention is probed in the evening, close to the hypothetical circadian wake-maintenance [59, 61, 62]. Furthermore, subjective mood also displays a circadian variation in concert with circadian changes in core body temperature (CBT) [60].

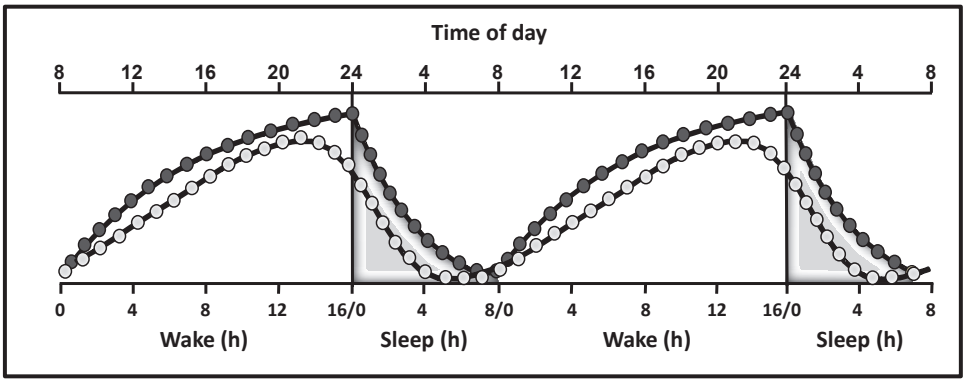

Figure 1. Schematic illustration of the two-process model of sleep-wake regulation (modified from Daan et al., 1984). The circadian process C (light grey) oscillates with a phase of nearly 24-hours independent of the prior sleep-wake history. Mainly reset by the light-dark-cycle, it promotes wakefulness and sleep under entrained conditions according to time of day. In contrast, the homeostatic process S (dark grey) increases with enduring wakefulness and declines during sleep relatively unaffected by the 24-hour cycle. In the end, the interaction of both processes determines the timing, the duration and the quality of sleep and wakefulness. *Figure and figure legend from Maire, Reichert & Schmidt, (2013), p.135.*

1.4 Impact on behaviour

As mentioned above behavioural variables, such as mood, well-being and subjective sleepiness, are linked to the duration of prior sleep and wakefulness and to circadian rhythmicity [59]. Cognitive performance was initially thought to reflect the impact of the circadian system, with minimal impact of prior sleep duration. In this context, performance was posited to decrease during the night and early morning, even if individuals were awake for less than 20-h [62, 63]. In a similar vein, performance would remain relatively stable in the evening, even if individuals were awake for more than 24-h [64, 65]. More recently, however, it was shown that, depending on the cognitive domain, performance may be linked to prior sleep and wakefulness [66, 67]. Sleep deprivation and chronic sleep restriction negatively impact on subjective sleepiness, mood, cognitive performance and quality of life [68-70]. Moreover, studies show that, in order to maintain performance across the entire day, young individuals need approximately 8 to 9-h sleep per day [69, 71].

1.5 Impact on physiology

Most human circadian physiological processes are modulated by the circadian clock, and depend on time-of-day [72, 73]. Key markers of the biological clock include plasma melatonin and cortisol, and core body temperature.

As mentioned above, melatonin is synthetized only during the night, thus indexing an individual's biological night [74]. Melatonin circadian rhythmicity is largely independent of prior sleep and wakefulness, and is most responsive to environmental light changes. The cortisol profile increases during the night and reaches maximal levels in the early morning before it decreases during the day [75, 76]. Cortisol secretion not only depends on the sleep/wake cycle [77] but also on other factors, such as stress and activity [78, 79], and light exposure [4, 80]. The circadian rhythm in core body temperature appears to be generated by periodic variations in heat production and heat loss [81]. Both heat production and heat loss are modulated by different activities, such as food intake, hormonal variation and the sleep-wake cycle

[82-84]. Body temperature is also related to cardiac activity [85], such that the greater the cardiac activity, the higher the body temperature [86]. In sleep deprivation protocol, only a small circadian variation was shown for heart rate (HR) variability, with lower levels during the night than during daytime[87]. Moreover, in everyday life, sleep processes exerted a predominant influence on the 24-h profiles with a decrease in HR during sleep periods independent of time of day [87]. However, it has been shown that the incidence of cardiovascular events followed a circadian variation, such that they occur more frequently in the morning hours [88, 89]. This may be related to exogenous factors that could precipitate adverse cardiac events [90, 91] as for instance, the transition between sleep and wakefulness. Thus, the cardiovascular events might be more dependent on the sleep-wake transition than on circadian rhythms *per se*.

2/ Impact of light on the human organism

2.1. Physical characteristics of the light

Speaking about light refers to light visible to the human eyes and responsible for the sense of sight. The properties of visible light include intensity, direction of propagation, frequency or wavelength spectrum, and polarisation, while its speed in a vacuum (*c*), 299,792,458 meters per second, is one of the fundamental constants of nature [92, 93]. Visual light comprises electromagnetic radiations (EMR) defined as having a wavelength in the range of 380 nanometers (nm) or $3{,}8.10^{-9}$ m to 760 nm ($7{,}6.10^{-9}$m), between the infrared (>760nm) and the ultraviolet (<380nm) [94] (**Figure 2**) and a frequency between 405 and 790 THz. The wavelength is inversely proportional to the wave frequency:

$$\lambda = \frac{v}{f}$$

where λ is the wavelength, v the speed of light and f the frequency.

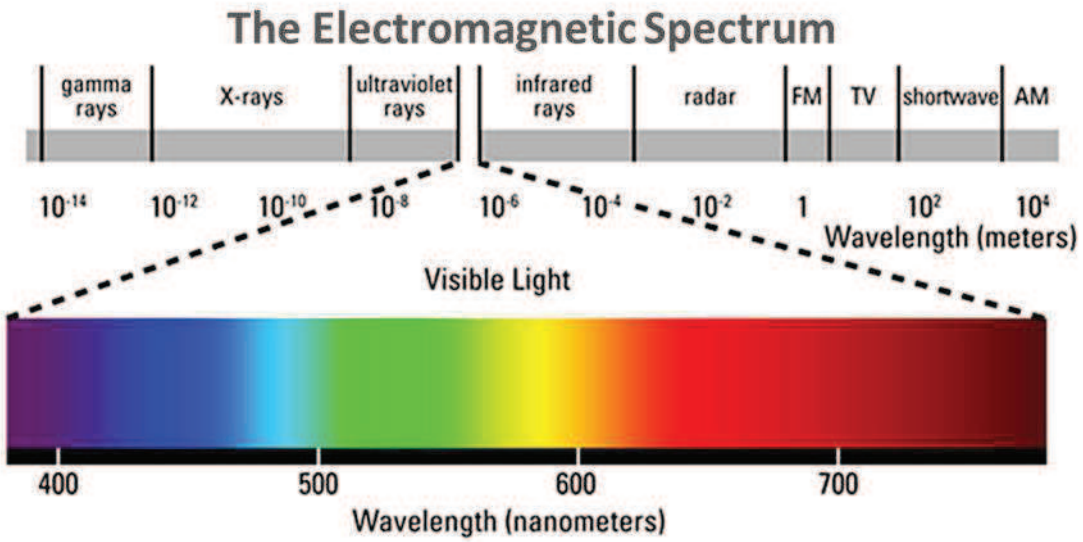

Figure 2: Visible spectrum of light for the human eye. *Figure from Kaiser* [95].

The EMR depends on its phase and its wavelength, where higher frequencies have shorter wavelengths and lower frequencies have longer wavelengths. The wavelength is responsible for the colour perception of the light; therefore, EMR comprising many waves at the same wavelength is called monochromatic.

There are three mains measure of light: (1) the **luminous flux**: a measure of the total "amount" of visible light emitted by a source, the unit is the Lumen (lm). It reflects the varying sensitivity of the human eye to different wavelengths of light. (2) The **radiant flux** (or power) indicates the total power of all electromagnetic waves emitted, independent of the eye's ability to perceive it. The SI unit of radiant flux is the watts (W). (3) The **light intensity**, with the unit candela (cd), is the power emitted by a light source in a particular direction, weighted by the luminosity function (or luminous efficiency). The candela is also defined as: 1cd= lm/sr, where sr or steradian, is the solid angle subtended at the centre of a unit sphere by a unit area on its surface [96, 97].

The luminous intensity for light of a particular wavelength λ is given by:

$$I_v(\lambda)=683.002\times\bar{y}(\lambda)\times I_e(\lambda)$$

where *Iv(λ)* is the luminous intensity in candelas, $I_e(\lambda)$ is the radiant intensity in watts per steradian (W/sr) and *y(λ)* is the standard luminosity function. If more than one

wavelength is present (as is usually the case), one must sum or integrate over the spectrum of wavelengths present to get the total luminous intensity.
The most common unit when we speak about light is lux (lx), the difference between the unit lumen and lux is that the lux takes into account the area over which the luminous flux is spread; mathematically, 1 lx = 1 lm/m^2.

The main interaction with matter in the visible range is with excitation of molecular electrons. When EMR interacts with single atoms and molecules, its behaviour depends on the amount of energy per quantum it carries [98, 99].
EMR in the visible light region consists of quanta (called photons) that are at the lower end of the energies that are capable of causing electronic excitation within molecules, which lead to changes in the bonding or chemistry of the molecule [97, 100]. Indeed, the atom goes from a ground state to an excited state by absorbing a photon of light and can also return to its ground state by emitting light, the color (wavelength) will depend on the energy levels of the atom [97]. Photon energy is directly proportional to the wave frequency.
At the lower end of the visible light spectrum, EMR becomes invisible to humans (infrared), because its photons no longer have enough individual energy to cause a lasting molecular change (a change in conformation) in the visual molecule retinal in the human retina, which triggers the sensation of vision [101, 102].

The colour emitted by a light source is measured by the degrees of Kelvin (K). The Kelvin colour temperature is defined by a black body surface being heated, such that at some point the object will get hot enough to begin to glow. The colour temperature of the light is the actual temperature of the surface, only if thermal radiations are emitted by a black body radiator. Only incandescent lamps can meet this truest definition of colour temperature [103]. The others, without thermal radiations (fluorescent light, LED, etc.), have what is referred to as a "Correlated Colour Temperature" (CCT). Correlations to any part of the colour temperature scale are strictly visually based [104].
Colour temperatures over 5000K are called cool colours (bluish white), while lower colour temperatures (3000 K) are called warm colours (yellowish white through red).

2.2. Structure of the eyes: Visual organ

2.2.1. The eyes

The eye allows us to see and interpret the shapes, colours, and dimensions of objects in the world by processing the light they reflect or emit. The eye is able to detect bright light or dim light, but it cannot sense an object when light is absent. Light waves from an object are perceived by the eyes and first enter through the cornea, then progress through the pupil, the circular opening in the centre of the coloured iris. Depending on light's intensity, the pupil size will change: they constrict or become smaller, with high intensity and dilate, or become larger, with low intensity [105]. After light has entered the pupil, it passes through the crystalline lens and the interior chamber of the eye to the retina, a thin membrane of cells on the outer wall, sensitive to changes in light. The lens of the eye focuses light on the photoreceptive cells of the retina, which detect the photons of light and respond by producing neural impulses. These signals are processed in a hierarchical fashion by different parts of the brain, from the retina upstream to central ganglia in the brain [105].

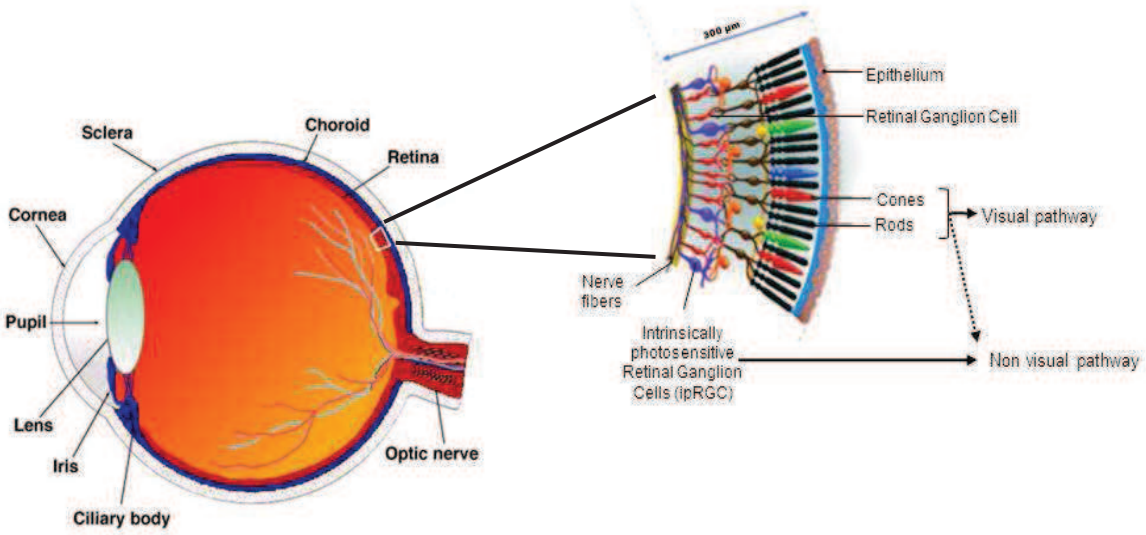

Figure 3: Principal eye structures and the cell constitution of the retina. *Figure and legend modified from [105] http://webvision.med.utah.edu*.

2.2.2. The retina

The structure of the retina has been known for many years and was clearly illustrated in 1900 by Santiago Ramon y Cajal. It lines the inner surface of the eye and is composed of nerve tissue which senses the light entering the eye. This complex system of nerves sends impulses through the optic nerve back to the brain, which translates these messages into images that we see.

The mammalian retina is composed of distinct types of cells organised in four main processing stages: photoreception, transmission to bipolar cells, transmission to ganglion cells which also contain photoreceptors, the photosensitive ganglion cells, and transmission along the optic nerve. At each synaptic stage, there are also laterally connecting horizontal and amacrine cells. The visual light activates specialized cells in the outer layer called rods and cones. The entire retina contains about seven million cones and 75 to 150 million rods (**Figure 3**) [105].

Both cells contain photopigments that can catch light energy or photon to convert it into a nervous signal; photo-opsin is present in the cones and rhodopsin in the rods. When light of the correct wavelength hits the photopigment, its electron will be excited and cause a change in the 3-D structure of the pigment as seen above. Due to this change in shape, the photoreceptor cell will send a nerve impulse to the brain and the pigment molecule will then return to its original 3-D shape to be able to be stimulated again [106].

The cones are mostly concentrated towards the macula, densely packed in the fovea centralis, and which is “rods free” (**Figure 4B**). They are responsible for colour vision, as well as eye colour sensitivity. They are less sensitive to light than rods, indicating that they function best in relatively bright light (photopic vision). However, their response time to stimuli is faster than those of rods, which allow them to track rapid changes in images. Humans have 3 subtypes of cones sensitive to different wavelengths: the short wavelength (S-cones), medium wavelength (M-cones) and long wavelength (L-cones) (**Figure 4A**) [107, 108]. That is why our vision is called trichromatic. Cones also tend to possess a significantly elevated visual acuity, as each cone cell has one connection to the optic nerve. [109].

Rods function in less intense light, are concentrated at the outer edges of the retina and used for peripheral and night vision (scotopic vision) [110, 111]. Because they have only one type of light-sensitive pigment (most sensitive to wavelengths of light around 498 nm (green-blue)) (**Figure 4A**), they have little, if any, role in coloured vision. Also, multiple rod cells converge on a single interneuron, which comes at a cost to visual acuity.

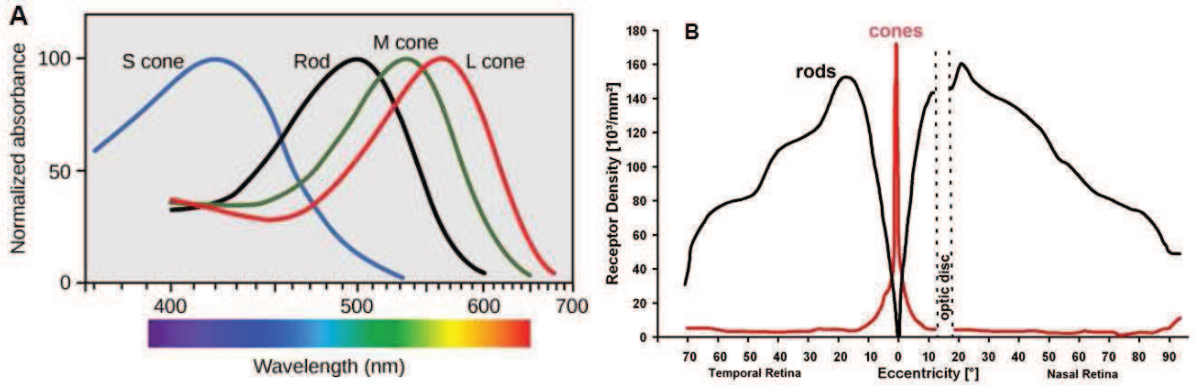

Figure 4: **(A)** Absorption spectrum from the 3 subtypes of cones; sensitive to short wavelength (S-cone or Blue cones), to medium wavelength (M-cones or Green cones) and to long wavelength (L-cones or Red cones) and from the rods. *Figure and legend modified from Bowmaker, 1980* [108] **(B)** Repartition of rods and cones density in function of the fovea angle in the retina. *Figure and legend modified from Osterberg, 1935 [112].*

Following synaptic transmission to the bipolar and amacrine cells, which help to organize information from rods and cones, visual light activates the retinal ganglion cells, which in turn communicate to the brain via the optic nerve. The ganglion cells lie innermost in the retina while the photoreceptive cells lie outermost. Because of this counter-intuitive arrangement, light must first pass through and around the ganglion cells and through the thickness of the retina, before reaching the rods and cones.

2.3. Light perception and connection to the brain

2.3.1. Visual pathway

As described above, shape, colour and movement perception go through rods and cones within the retina. These photoreceptors convert the light signal into an electrical signal, which is then transmitted to the retinal ganglion cells. The latter sends this information via the optic nerve to the higher cerebral areas where the integration and the conscious visual perception occur. About 90% of the axons in the optic nerve go to the lateral geniculate nucleus in the thalamus. Another population sends information to the superior colliculus in the midbrain, which assists in controlling eye movements, as well as other motor responses. Neurons of the lateral geniculate nucleus (LGN) then relay the visual image to the primary visual cortex (V1), located in the occipital lobe (**Figure 5**) [113]. Indeed, destruction of cone cells due to disease can result in colour blindness, which has a prevalence as high as 5% in the general population.

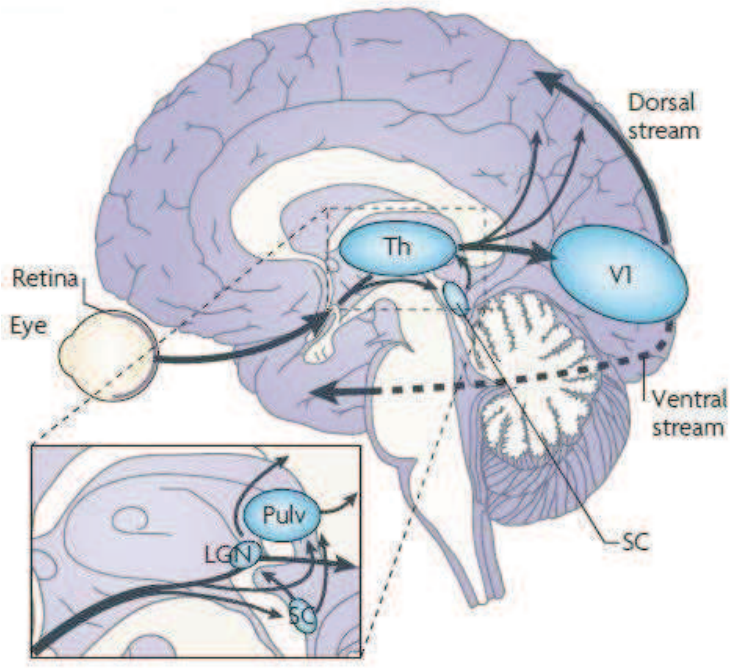

Figure 5: Cortical and subcortical pathways for vision. The primary visual pathway (shown by thick arrows) originates from the retina and projects to the primary visual cortex (V1) in the occipital lobe via an intermediate station in the lateral geniculate nucleus (LGN) of the thalamus (Th). From V1, visual information reaches the extrastriate cortex along the ventral (occipitotemporal) and the dorsal (occipitoparietal) stream. However, a minority of fibres originating from the retina take a secondary route (shown by thin arrows) and reach both the superior colliculus (SC) and the pulvinar (Pulv). These two subcortical sites are connected and also send direct projections to the extrastriate visual cortex, bypassing V1. Another V1-independent visual pathway consists of the direct projections between the superior colliculus and the LGN that, in turn, send efferents to extrastriate cortices in the dorsal stream. *Figure and legend from* [3].

2.3.2. Non-visual pathways

However, beside rods and cones, the circadian entrainment involves other photoreceptors, which were discovered in the nineties [114, 115], and who are responsible of the non-image forming (NIF) effect or non-visual effect of light. They are called intrinsically photosensitive retinal ganglion cells (ipRGC) [116-119] (**Figure 3**) and contain the photopigment melanopsin [120]. Melanopsin is an opsin similar to the one found in rods and cones but is more sensitive to blue light. These ipRGC receptors are a third class of retinal photoreceptors, excited by light even when all influences from classical photoreceptors (rods and cones) are blocked [121] and represent 1-3% of the retinal ganglion cells. They are maximally sensitive to short wavelength (460-480nm, blue light), unlike conventional visual receptors (<550nm, green light) [5, 12, 122] (**Figure 6**). They are present in low densities throughout the retina and the non-visual effect of light will act principally through this channel [123].
There is growing evidence that the classical rod and cone photoreceptors also contribute to the NIF light responses in human [124].

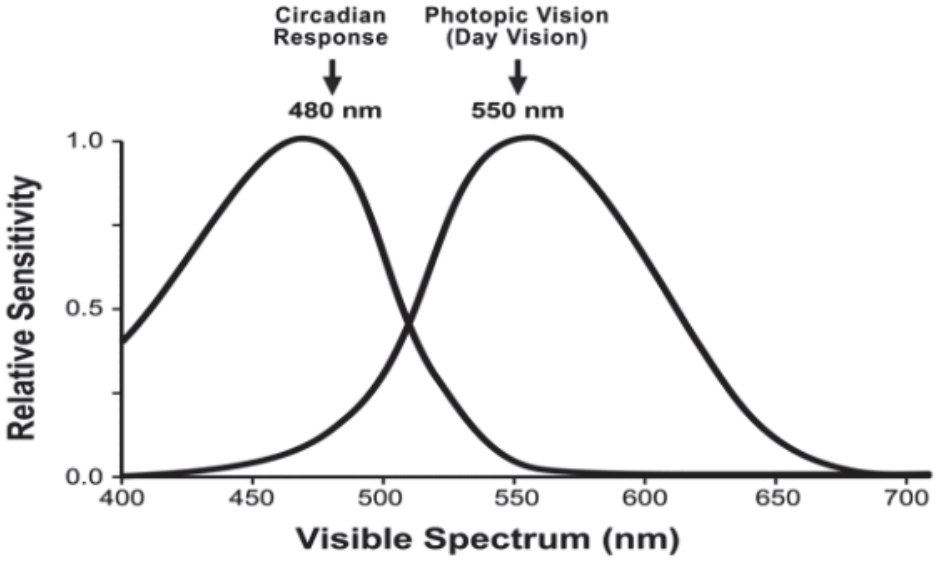

Figure 6: Absorption spectrum from the intrinsically photosensitive retinal ganglion cells (ipRGC) compared to the visual response. *Figure from Roberts, 2010* [1].

A specialized non-visual retinohypothalamic tract (RHT) provides direct neuronal connection to the SCN, which innervates several brain correlates mostly located within the thalamus and hypothalamus, with indirect projection to the ventro-lateral preoptic nucleus (VLPO) containing active neurons during sleep, and to the lateral hypothalamus (LH) containing cell bodies of orexin neurons regulating wake [125]. Projections to the olivary pretectal nucleus (OPN) are involved in the pupillary constriction, to the lateral habenula (LHb), which is a relay site between limbic and striatal regions and the midbrain, to the amygdala (AM) involved in the regulation of emotion, to the intergeniculate tractus from the thalamus (IGL) and to visual regions, such as the hypothalamus lateral geniculate nuclei (LGv/d) and the midbrain superior colliculus (SC), which has a variety of functions including control of eye movements and sleep regulation. One of the weakest projections is to the subparaventricular zone (SPVZ), involved in regulating body temperature and food-energy intake [117, 126] (**Figure 7**).

The SCN also communicates indirectly with the locus coeruleus (LC) in the brainstem. Because of its thalamic and cortical connections, it influences the modulation of the network involved cognitive performance. Subcortical regions are activated more rapidly and are responsible for short-term effects of light, while the long-term effects and cortical responses related to task performance appear when exposure to light is longer and with higher intensity [127].

In humans, light is intuitively related to the alert phase unlike nocturnal animals where the light phase corresponds to the resting state. Thus, the human visual system matches the diurnal species' need for vision but also for the non-visual effect of light. Therefore, hormonal secretion, heart rate, body temperature, sleep, alertness, pupillary constriction and gene expression are directly influenced by the light in order to adapt themselves to the light/dark cycle [25-27].

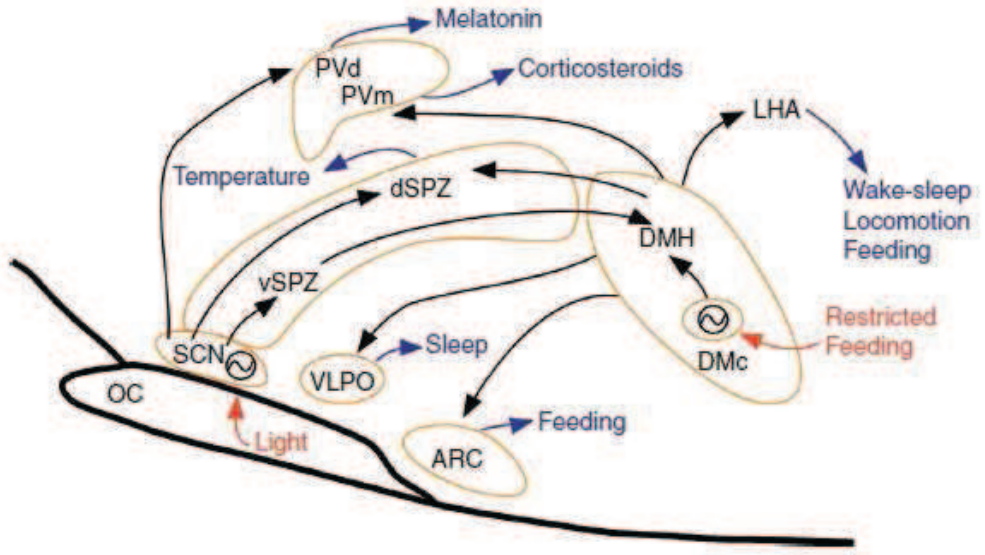

Figure 7: A schematic drawing showing the main components of the circadian timing system in the mammalian brain. Arrows show neural pathways that convey these influences, but do not imply whether they are excitatory or inhibitory, which in some cases is not known. The neurons of the suprachiasmatic nucleus (SCN) form a genetically based clock which is reset daily by the light cycle. The SCN drives some circadian rhythms, such as that of melatonin, by direct outputs to target cell groups such as the paraventricular nucleus (PV), but most circadian rhythms are mediated by relays through the subparaventricular zone (SPZ).
DMH, dorsomedial nucleus of the hypothalamus; ARC, arcuate hypothalamic nucleus; OC, optic chiasm; PV, paraventricular hypothalamic nucleus; PVd, dorsal parvicellular PV; PVm, medial parvicellular PV; nucleus VLPO, ventrolateral preoptic nucleus. Zeitgebers are in red; cell groups outlined in tan; circadian functions in blue. *Figure and legend from [128]*.

2.4. Functions of the light

The central clock is crucial for the synchronisation of the environmental cycles in response to light. These non-visual effects of light are necessary for the synchronisation between the internal circadian timing and the external timing (24-h earth rotation) [129]. Thus, an attenuation of this “Zeitgeber” or its occurrence in an inappropriate timing can lead to an inappropriate synchronisation of these two variables.

Some studies have shown that a light pulse administered at different times during the day lead to a fast expression of clock genes within the SNC [130], which may induce circadian phase shifts. Specifically, while evening light exposure induces a delay in sleep onset, morning light exposure results in a phase advance [131]. A phase

response curve (PRC), reflecting the phase shift in function of the time of light exposure, allows to define at what time-of-day it is better to be exposed to light depending on the purpose of light exposure [132, 133] (**Figure 8**). Furthermore, our organism also reacts differently depending on the intensity and wavelength of the light, as well as the duration and timing of exposure.

Since the eyelids have a filtering effect and allow only 5% of the light intensity to pass through [134], the NIF effects will be more pronounced when the eyes remain open during light exposure. In addition, only the light rays of long wavelength will be transmitted through the eyelids [135].

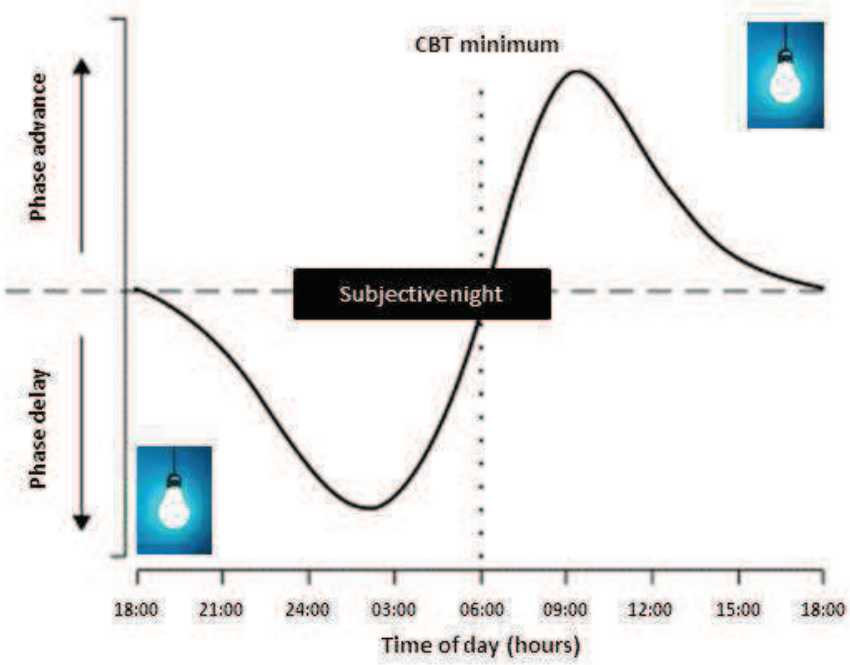

Figure 8: Phase response curve (PRC) of a human being, in response to light. Subjective night (i.e., night-time according to the biological clock) is indicated by a black horizontal bar. Maximum phase shifts are within 4–5 h of the time of core body temperature (CBT) minima. The precise shape and amplitude of PRCs for humans depend on the strength (i.e., intensity and duration) of the light stimulus. Figure and figure legend m*odified from [2]*.

3/ Modulations of the impact of light

3.1. Environmental disturbances

Large individual differences are found in humans for their preferred [136] or actual [137, 138] sleep-wake timings. These differences pertain to our chronotype, which can be early (morning type), intermediate or late (evening type). Extreme early types are characterized by going to bed and waking-up early, especially during free days (22:00–06:00 h), whereas late types do the opposite (04:00–12:00 h), based on Dutch general population data [139]. Nowadays, work and social requirements enforce supplementary difficulties, especially for both extreme types. This misalignment between the external and internal clock is called “social jetlag”. The prominence of this social jetlag is significantly correlated with mental distress, and unhealthy behaviours, such as the tendency to smoke and to consume alcohol [140]. One of the consequences of this phase shift is impairment in daily tasks when executed early the morning for the evening chronotype and late in evening for the morning chronotype.

During the period immediately after waking-up, people may suffer from confusion, disorientation, sleepiness and grogginess, and cognitive and physical performances may not be optimal. This transitory process is called “sleep inertia” [141, 142]. This “weakening of performance” during the first hours after waking-up are states that are experienced by most people to some extent. The severity and duration of this state varies depending on sleep structure, sleep stage prior to awakening, as well as circadian phase [142, 143].

Sleep inertia occurs at all times of day and night [144] and after different sleep durations [145, 146]. After one hour, subjective sleepiness and cognitive performances rapidly improve and sleep inertia dissipates progressively [145]. After 8-h sleep duration, sleep inertia effects are modest and short, however cognitive performances straight after waking-up are worse than after a total sleep deprivation night [147].

The lack of daylight during the winter time can also lead to an aggravation of sleep inertia due to the deficiency of the morning light phase advance [133, 148, 149] and to the dramatic reduction of its simulating effects [11, 150, 151].

3.2. Social disturbances

Circadian rhythm disturbances are frequently encountered in our society, because of the modern life condition (night and shift work, transmeridian travel, etc.) and the general aging of the population. The desynchronisation between environmental and internal rhythm leads, in the long term, to pathological states, such as sleep disorder, obesity, cardiovascular dysfunction and/or cancers. Short-term effects can also be observed, including an increase of sleepiness, a decrease of alertness and cognitive performances as well as a decrease in subjective mood.
As bright light exposure stabilises the sleep/wake cycle, improves synchronisation of the circadian rhythm and prevents from detrimental effects of night work on sustained attention [152], it can be used as a countermeasure to counteract a circadian shift when applied at a specific time [153]. Furthermore, it has also been shown that light exposure significantly reduces the mental capacity decline in elderly dementia people [154], thus enhancing cognitive performance.

Nevertheless, light exposure can have deleterious effects on circadian rhythms when applied at an inappropriate time. Moreover, artificial light sources in our surrounding environment (light pollution) are not well appropriate, as it can disturb sleep [155]. Similarly, the use of LED screens the evening before going to bed can delay our internal rhythm and sleep latency and disturb our sleep [156, 157].

3.3. Aging

Aging is associated with numerous changes in the sleep-wake cycle, such as an increased number and duration of awakenings, less slow waves sleep and a greater amount of daytime naps [158, 159]. Sleep quality is also affected, with more sleep disorders reported such as insomnia or sleep apnea [158, 159]. Aging is also associated with a decrease in psychomotor vigilance performance (i.e. increase in reaction time) and impaired learning capacities [17, 59].

Sleep problems in the older population may arise from age-related changes in homeostatic sleep mechanisms [160] and/or alterations in components of the circadian system, including reduced circadian rhythm amplitude and advanced circadian phase [161-163]. Age-related changes in the phase relationship between sleep and the rhythm of endogenous melatonin [162] may also contribute to disturbed sleep. Quantitative evidence for a dampened circadian arousal signal in older individuals was observed through increased sleep in the wake maintenance zone [163] and lower levels of melatonin secretion.

These changes do not suddenly appear at an age of 60 years, but gradually start to occur during the middle years of life [164]. Since light perception changes with ageing, it is very likely that the input level (i.e. the eyes) plays a major role in possible circadian alterations with ageing. Many age-related changes have been described in the eye including optical or neural features that can lead to a reduction in retinal sensitivity to light [165, 166]. Aging is also associated with a reduced pupil size [167], an increased lens density [168-170], causing an alteration in the spectral absorption, as well as a darkening of the lens and a development of a yellow pigmentation that further reduces light transmission to the retina. Lens absorption is more pronounced for short wavelength light that is optimal for appropriate entrainment of the endogenous biological clock [171]. As a result, the levels of light reaching the retina can be reduced, leading to less photic entrainment of the circadian clock, which could explain some changes in the elderly. Furthermore, due to the loss in ganglion cell numbers with age [172], older individuals may need a higher intensity of light exposure to express a similar effect as the young.

3.4. Genetic predisposition

All these disturbances reveal large inter-individual differences in sleep and circadian rhythmicity and led to the question as to what is driving these individual differences [173]. Due to progress in research of genetic and molecular basis of sleep and circadian rhythmicity, some genes contributing to inter-individual differences in sleep architecture, timing, and duration in humans and mice have been pointed out [174-176]. Among these, a number of gene have been implicated in the generation of circadian rhythms, so called “clock genes”. The Per gene family belongs to the most prominent of these. These genes are involved in a complex molecular feedback loop setting the period of the oscillator.

The coding region of the *PERIOD3* (*PER3*) gene contains a primate specific variable-number tandem-repeat (VNTR) polymorphism in which a motif encoding 18 amino acids is repeated either four ($PER3^{4}$) or five times ($PER3^{5}$) [177]. This polymorphism has been related to sleep loss related vulnerability in humans [18, 19]. It has also been linked to delayed-sleep-phase syndrome (DSPS) and diurnal preference, such that homozygosity for the 5-repeat allele ($PER3^{5/5}$) was associated with extreme morning preference (i.e. early chronotype), while homozygosity for the 4-repeat allele ($PER3^{4/4}$) was associated with extreme evening preference (i.e. late chronotype) [177-179]. The $PER3^{4/4}$ have also been reported to be more resilient to the detrimental effects of sleep deprivation than the $PER3^{5/5}$ individuals [19, 178]. Others studies show evidence for higher vulnerability of the long allele carriers regarding sleepiness [180] and cognitive function [18-20].

In parallel, it was shown that *PER3* polymorphism has a differential impact on cognitive brain responses to light [21], on melatonin suppression and on subjective alerting effect of light [22], and sleep regulation (Chellappa et al., 2014), such that the homozygous carriers of the long repeat allele ($PER3^{5/5}$) are more sensitive to blue light. In other words, when individuals are under high homeostatic sleep pressure, light elicits stronger activating effects for those who are genetically succeptible to sleep loss.

4/ Light as a countermeasure of these disturbances

Light impacts on behaviour by improving or deteriorating well-being, mood, alertness, sleepiness and cognitive performance, and on physiology, by increasing or decreasing the core body temperature, by modulating melatonin and cortisol profile and by inducing a phase shift [5-7].
However the extent of these effects strongly depend on light characteristics, particularly the timing and duration of exposition, intensity, wavelength and dynamics of light exposure.

4.1. Timing of the exposure

Due to the filtering effect of eyelids, it is problematic to test light effects during sleep [134, 135]. Thus, light effects impacting onto sleep are typically timed prior to an individual's sleep-time. Accordingly, one of the main responses to light exposure at night is melatonin suppression, which may result in increased alertness and decreased markers of fatigue (e.g. slow eyes movement).
However, a recent study [181] showed that light flash during sleep is able to shift the timing of the circadian clock without major alterations to sleep itself. Given confirmation that the flashes penetrated the eyelids.
The effect of light on physiology (melatonin expression, core body temperature, heart rate) depends on the timing of exposure, such that a night light exposure can impact onto these variables more robustly than a daylight exposure. Conversely, its effects on psychological variables (subjective sleepiness, mood) seems to be rather independent of the timing of exposure [151]. Furthermore, it was also demonstrated that light can modulate subcortical structures activity responsible for vigilance and thus actively promote cortical activity in networks involved in non-visual cognitive processes independent of time [16].

4.2. Light duration

Light effects do not automatically increase with the duration of exposure. Indeed, Eastman and colleagues showed that 6-h of light exposure has the same effect on the circadian rhythm compared to 3-h of light exposure [182]. Moreover, intermittent bright light was shown to exibit the same phase shifting than continous bright ligh exposure, eventhough the duration of the intermittent bright light exposure represent only 63 or 31% [183], or even 23% [184] of the continous light exposure. More recently, Zeitzer and colleagues demonstrated that milliseconds of flash are also sufficient to phase shift the human circadian clock and to observe immediate alerting effect [185]. Thus, humans should exhibit an enhanced sensitivity to the initial minutes of bright-light exposure.

4.3. Light intensity

One may intuitively assume that the effects of light are directly proportional to its intensity. However, this is not the case, as the effect on alertness and melatonin supression obtained at 9000lux is virtually the same as for 3000lux. Indeed, light exposure at 100lux is enough to reach 50% of the effect achieved at 9000lux [11, 186, 187]. Even if the response threshold is between 50-100lux, 150 lux is enough to observed changes on physiological and behavioural level.
The natural daylight at noon is around 100000lux, which explain why the sunlight is the most effective “Zeitgeber” for the organism.

4.4. Light Wavelength

The wavelength of light also modulates the non-visual light responses in humans. As mentioned above, the visible light spectrum ranges from 400nm to 700nm and ipRGC have maximal sensitivity at around 460-480 nm. Indeed, melatonin suppression and increased alertness, body temperature and heart rate after light exposure are more sensitive to light of short wavelength (in blue) compared to a light of higher wavelengths (i.e. green or orange) for which the effects are less or almost non-existent [5, 188].

4.5. Dynamic of light exposure

Recently, the dynamcis of light, or how light evolves across time, was shown to play a key role in the effects of light onto behaviour and physiology. In broad terms, light is directly switched on at wake-up time, such that light increases by several lux at once. Another “type of light” was then developed, in which light intensity increases gradually before the alarm and remains at the desired level a few minutes after an audible alarm clock. By changing this dynamics, it is possible to modify the behavioral component during the first hours after wake-up time. In other words, waking-up with the dawn simulation light may thus reduce subjective sleepiness, enhance well-being and reduce sleep inertia compared to waking-up with a control light [80, 189]. Furthermore, physical well-being and cognitive performance (as indexed by faster reaction times) are improved [190].

Dawn simulation light is also more effective than bright light exposure in the morning for the treatment of patients with seasonal affective disorder (SAD) or winter depression [191-193].

For several years, researchers have used light as a mean to counteract some of the detrimental effects of the modern life (e.g., night and shift work, transmeridian travel, etc.). They discovered that nightime light exposure suppresses melatonin profile and delays circadian rhythms, but may also improve subjective sleepiness, mood and cognitive performance. Daylight exposure has also been shown to enhance subjective sleepiness, mood and cognitive performance, with a concomitant melatonin phase advance when applied during the morning hours. Some studies have even demonstrated that by changing the dynamics of the light at wake-up time it is possible to reduce sleep inertia. However, if this dawn simulation light can enhance our performance during the day was not been investigated to date. It also remains to be fully understood if a sustained (long-term) light exposure can “boost” our performance and sleepiness even further or whether a “plateau” is reached after certein duration. Another open question is if long-term light exposure can modulate physiology, as indexed by melatonin and cortisol profiles, and body temperature. Thus, the focus of this thesis was to answer these questions and to understand how individual differences may underscore these effects of light.

III- Objectives of the thesis

The principal aim of this work was to **investigate the impact of light and its different characteristics on neurbehavioural and circadian physiological parameters in healthy volunteers, and how this light effect is modulated by inter-individual differences, such as aging and a genetic predisposition**.

To answer these questions, we first investigated **whether a morning light exposure can counteract the detrimental effects of 6-h sleep restriction on neurobehavioural and circadian physiological outcomes in young participants**. We focused on the dynamics and the timing of morning light exposure and investigated the impact of morning artificial dawn simulation light exposure (**Figure 9**) on alertness, well-being, mood, cognitive performance, and classical markers of the circadian timing system (melatonin and cortisol) in comparison to a dim light control condition, as well as to a bright monochromatic blue light exposure of fixed intensity (**Figure 10**), known to impact on human physiology.
In a second step, we aimed at answering whether dawn simulation light following sleep restriction enhances performance according to cognitive domain in the morning, and whether these effects are sustained for the remainder of the day.

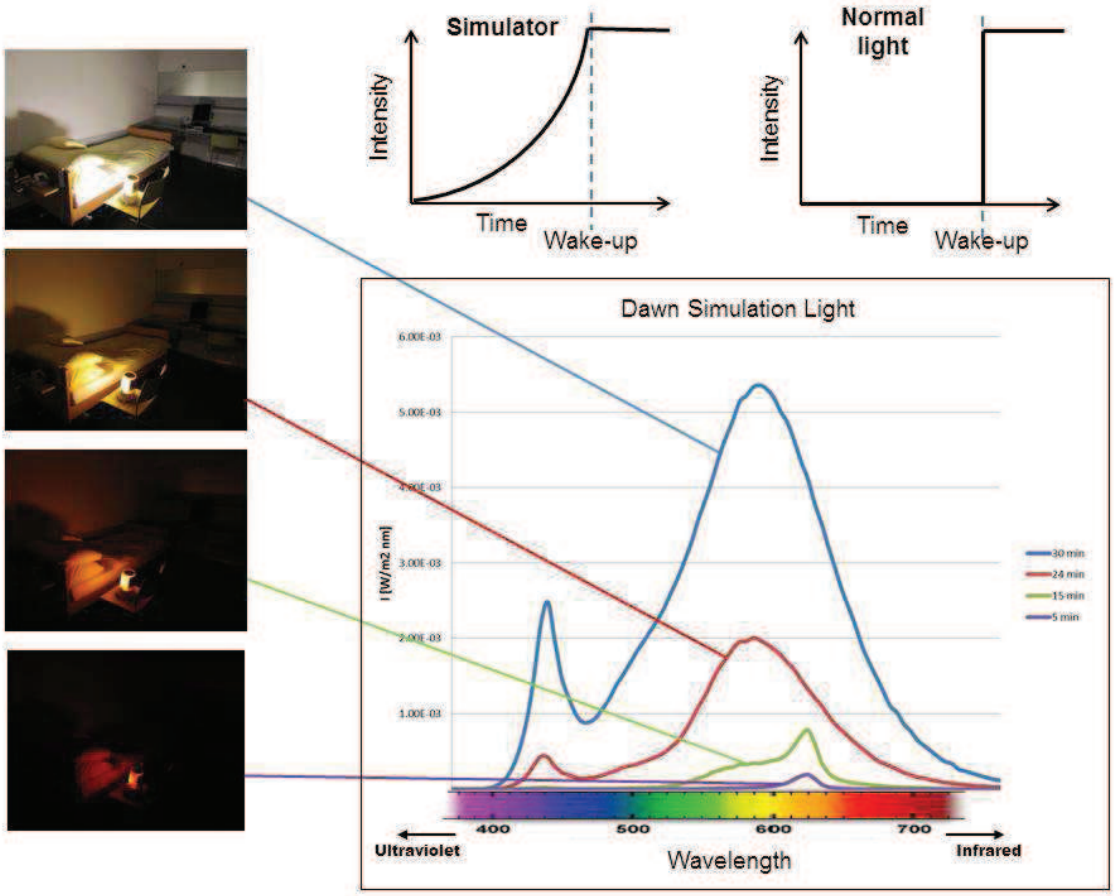

Figure 9: Dynamic differences between a dawn simulation light and a normal light On/Off. Spectral composition (light wavelength by irradiance; W/m^2-nm) of the dawn simulation light at 5 min (violet line), 15 min (green line), 24 min (red line) and 30 min (blue line).

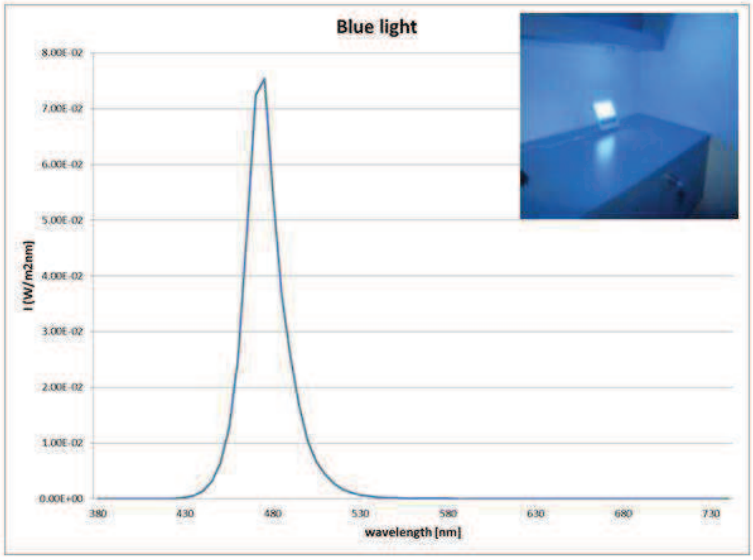

Figure 10: Spectral composition (light wavelength by irradiance; W/m^2-nm) of a monochromatic blue light

In a third step, we focused on the duration and wavelength of the light. Our main question **was whether a long-term 40-h light exposure further improves cognitive performance, sleepiness, and modulates circadian physiological variables, and how this light effect is modulated by inter-individual differences, such as aging and a genetic predisposition**. To do so, we implemented a 40-h sleep deprivation protocol under either white light or blue-enriched white light exposure compared to a dim light exposure (**Figure 11**).

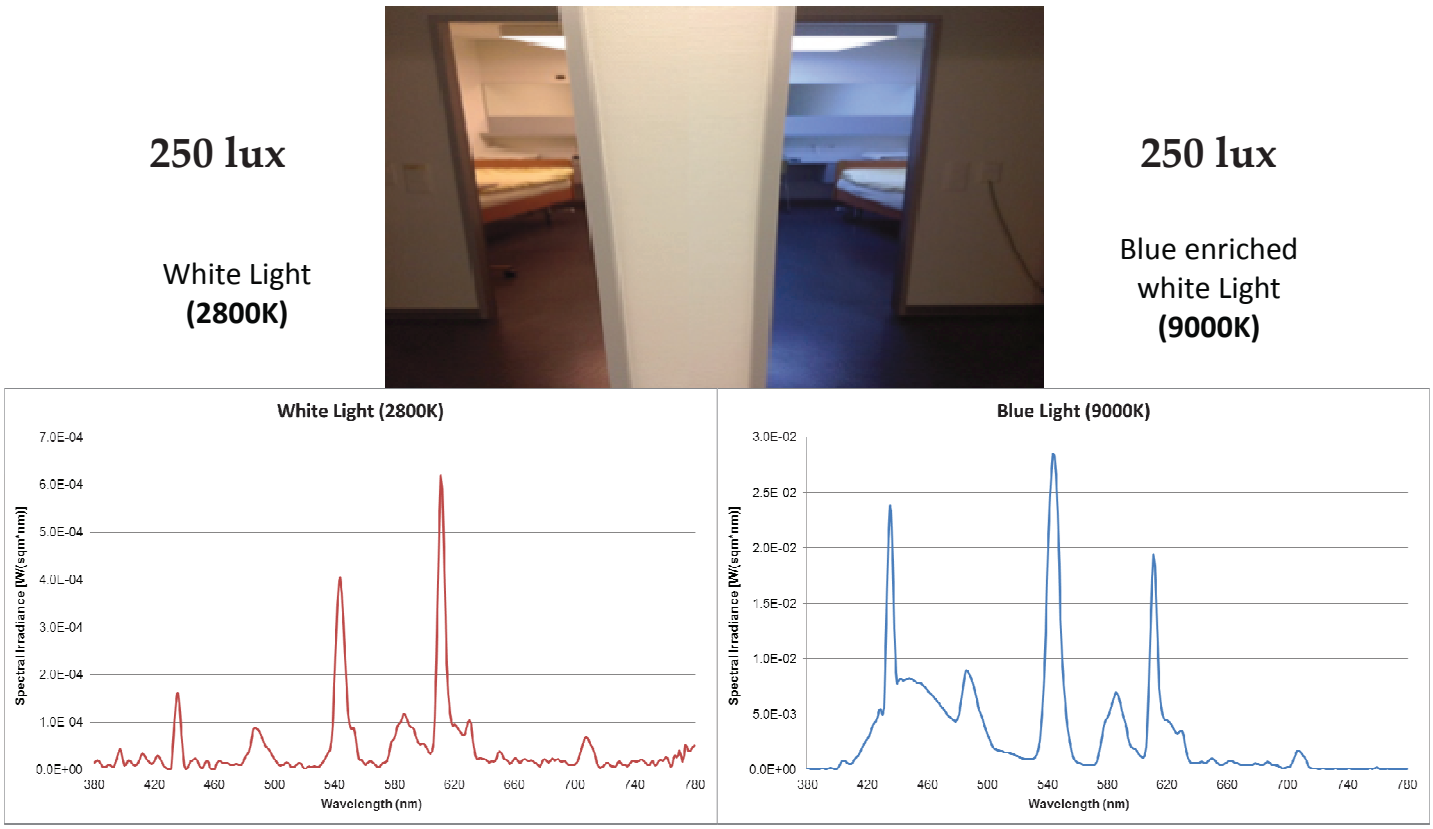

Figure 11: Spectral composition (light wavelength by irradiance; W/m^2-nm) of a polychromatic white light (left panel) and a blue enriched polychromatic white light (right panel)

The following 2 chapters will comprise five publications, which I co-authored as first author.

IV-Morning light effect in young study volunteers

1/ Circadian physiology

Effects of artificial dawn and morning blue light on daytime cognitive performance, well-being, cortisol and melatonin levels.

Dawn Simulation Light: A Potential Cardiac Events Protector.

2/ Neurobehavioral performance (cognition)

Dawn simulation light impacts on different cognitive domains under sleep restriction.

V-Extended light exposure

1/ Age dependent effects on circadian physiology and alertness

Differential impact of blue-enriched white light exposure on circadian physiology and alertness during sustained wakefulness in young and older individuals.

2/ A genetic predisposition (i.e. PER3 polymorphism) and circadian physiology and cognition

Light effect on neurobehavioural and circadian physiological variables depend on inter-individual differences.

IV- Morning light effect in young study volunteers

1/ Circadian physiology

Effects of artificial dawn and morning blue light on daytime cognitive performance, well-being, cortisol and melatonin levels.

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Effects of Artificial Dawn and Morning Blue Light on Daytime Cognitive Performance, Well-being, Cortisol and Melatonin Levels

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Light exposure elicits numerous effects on human physiology and behavior, such as better cognitive performance and mood. Here we investigated the role of morning light exposure as a countermeasure for impaired cognitive performance and mood under sleep restriction (SR). Seventeen participants took part of a 48h laboratory protocol, during which three different light settings (separated by 2 wks) were administered each morning after two 6-h sleep restriction nights: a blue monochromatic LED (light-emitting diode) light condition (BL; 100 lux at 470 nm for 20 min) starting 2 h after scheduled wake-up time, a dawn-simulating light (DsL) starting 30 min before and ending 20 min after scheduled wake-up time (polychromatic light gradually increasing from 0 to 250 lux), and a dim light (DL) condition for 2 h beginning upon scheduled wake time (<8 lux). Cognitive tasks were performed every 2 h during scheduled wakefulness, and questionnaires were administered hourly to assess subjective sleepiness, mood, and well-being. Salivary melatonin and cortisol were collected throughout scheduled wakefulness in regular intervals, and the effects on melatonin were measured after only one light pulse. Following the first SR, analysis of the time course of cognitive performance during scheduled wakefulness indicated a decrease following DL, whereas it remained stable following BL and significantly improved after DsL. Cognitive performance levels during the second day after SR were not significantly affected by the different light conditions. However, after both SR nights, mood and well-being were significantly enhanced after exposure to morning DsL compared with DL and BL. Melatonin onset occurred earlier after morning BL exposure, than after morning DsL and DL, whereas salivary cortisol levels were higher at wake-up time after DsL compared with BL and DL. Our data indicate that exposure to an artificial morning dawn simulation light improves subjective well-being, mood, and cognitive performance, as compared with DL and BL, with minimal impact on circadian phase. Thus, DsL may provide an effective strategy for enhancing cognitive performance, well-being, and mood under mild sleep restriction.

Keywords: Cognitive performance, cortisol, melatonin, morning light, sleep restriction, well-being

INTRODUCTION

Light exerts powerful non-image-forming (NIF) effects on behavioral and physiological functions, including hormonal secretion (Cajochen, 2005; Jung et al., 2010), sleep-wake regulation (for a review, see Chellappa et al., 2011a), cognitive function (Cajochen et al., 2011; Chellappa et al., 2011b), and its underlying cerebral correlates, encompassing cortical and subcortical brain regions (Vandewalle et al., 2009b). These light-dependent effects are to a large extent mediated by retinal photoreceptors containing the photopigment melanopsin, which are distinct from rods and cones (Hattar et al., 2002). Maximal sensitivity of the human alerting response and melatonin suppression to light occurs at the short-wavelength light (ca. 460–480 nm), contrasting with the spectral sensitivity of classical visual photoreceptors (green light, <550 nm) (Cajochen et al., 2005; Lockley et al., 2006; Münch et al., 2006; Revell et al., 2006). Together with light's wavelength, other properties, such as intensity, duration, and timing, are crucial in determining its effects on human physiology and behavior (for a review, see Cajochen, 2007). Nighttime light exposure triggers melatonin suppression with concomitant reduction of subjective sleepiness and objective markers of sleepiness (e.g., waking electroencephalographic [EEG] theta activity, incidence of slow eye movements) (Cajochen et al., 2000; Chellappa et al., 2011b, 2012; Lockley et al., 2006; Ruger et al., 2005). It has been suggested that these effects are mediated through melatonin's alerting effects and/or its resetting

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properties on the endogenous circadian pacemaker (Chellappa et al., 2011a). Although the studies investigating the impact of daytime light are less abundant, three studies reported that bright white light exposure during daytime also enhances alertness (Phipps-Nelson et al., 2003; Ruger et al., 2005; Smolders et al., 2012). In the same vein, 20 min of daytime exposure to bright white light (ca. 7000 lux) increases task-related cortical activity while performing an oddball paradigm (Vandewalle et al., 2006). Bright white light sources are used as a therapeutic countermeasure against circadian rhythm sleep disorders (Zhu & Zee, 2012) and depression, particularly seasonal depressive disorder (Wirz-Justice et al., 1986). Apart from its therapeutic use, bright light also improves well-being, vitality, and mood stability among healthy subjects working indoors in wintertime (Partonen & Lonnqvist, 2000). Furthermore, chronic daytime exposure to blue-enriched moderate-intensity light has the potential to improve visual comfort, alertness, sleepiness, and mood in the working environment (Viola et al., 2008).

More recently, the dynamics of light exposure have been shown to directly affect the impact of morning light exposure on sleep inertia, well-being, and cortisol levels (Gimenez et al., 2010; Van de Werken et al., 2010). The use of an artificial dawn light resulted in a significant reduction of sleep inertia complaints, which could not be explained by a shift in the dim light melatonin onset or timing of sleep offset (Gimenez et al., 2010). In another study, Van de Werken et al. (2010) showed that 30 min of an artificial dawn light (maximum 300 lux) prior to wake-up time was more efficient in alleviating sleep inertia and increasing subjective alertness compared to acute light exposure (300 lux) at wake-up time. However, they could not find significant effects on cognitive performance and did not confirm enhanced cortisol levels upon awakening after dawn, as observed earlier by Thorn et al. (2004). Although these initial studies clearly showed beneficial effects of an artificial dawn signal on sleep inertia and well-being, the design of the studies did not allow for testing how these acute effects of a dawn simulation light translate into daytime cognitive performance and well-being levels.

To address this question, we investigated the impact of morning artificial dawn simulation light exposure on alertness, well-being, mood, cognitive performance, and classical markers of the circadian timing system (melatonin and cortisol) and compared this effect with a dim light condition, as well as with a bright monochromatic blue light exposure of fixed intensity. The duration of light exposure during scheduled wakefulness (eyes open) was the same for each of the two experimental light conditions, but they differed in intensity, spectral composition, and the timing of administration. This latest aspect was motivated by the potential modality of using blue light not directly in the bedroom but at the beginning of the morning, possibly at work. One primary aim of this was to compare two morning light devices that are known for their effects on mood and cognitive performance, even though they do not share the same characteristics. The entire study protocol was performed under stringently controlled laboratory conditions, with two sleep restriction nights in order to test whether these light effects can counteract the detrimental effects of partial sleep loss on daytime alertness and cognitive performance, which is increasingly encountered in contemporary society. We hypothesized the following:

(1) As compared with the dim light condition, light exposure mimicking dawn will facilitate the wake-up process with respect to subjective perception of sleepiness, tension, and well-being and will have a beneficial impact on cognitive performance levels, especially in the time zone surrounding the wake-up period.
(2) As compared with the dim light condition, blue light exposure will increase subjective and objective neurobehavioral performance, which will be potentially sustained throughout the entire waking day.
(3) As maximal circadian phase-advancing properties have been attributed to short-wavelength light in the morning, particularly BL will lead to a advance in the assessed circadian phase markers (melatonin and cortisol).

MATERIALS AND METHODS

Study Participants

Study volunteers were recruited through advertisements at different local universities and internet sites in Switzerland, Germany, and France. The screening procedure began with a telephone interview, involving a detailed explanation of the study. All participants gave written informed consent. The study protocol, screening questionnaires, and consent forms were approved by the local ethics committee (EKBB/Ethikkommission beider Basel, Switzerland). They conformed to the Declaration of Helsinki and were performed in accordance with international ethical standards (Portaluppi et al., 2010). All applicants completed questionnaires about their sleep quality, life habits, and health state. These questionnaires comprised a consent form, a General Medical Questionnaire, the Beck Depression Inventory II (BDI-II) (Beck et al., 1961), the Epworth Sleepiness Scale (ESS) (Johns, 1991), the Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) (Horne & Östberg, 1976), the Munich Chronotype Questionnaire (MCTQ) (Roenneberg et al., 2003), and the Pittsburgh Sleep Quality Index (PSQI). Potential candidates with a PSQI score >5 were excluded from the study (Buysse et al., 1989). Further exclusion criteria were smoking, medication or drug consumption, body mass index <19 and >28 kg/m^2, shiftwork within the last 3 months, transmeridian flights during the 3 months before the study, as well as medical and sleep disorders. Since our

TABLE 1. Characteristics of the group of participants.

Characteristic	Minimum	Maximum	Mean ± SEM
n			17
Age	20	33	23.12 ± 0.82
Sleep time (h)	21:45	2:00	23:50 ± 00:19
Wake time (h)	6:00	10:00	07:57 ± 00:15
Sleep duration (h:min)	7:00	9:00	08:06 ± 00:08
BDI	0	7	1.47 ± 0.51
ESS	1.5	14	5.79 ± 1.01
MEQ	29	74	54.35 ± 2.64
MCTQ	2.33	6.49	4.4 ± 0.28
PSQI	1	5	2.88 ± 0.27
BMI	20.75	25.76	22.86 ± 0.35

BDI = Beck Depression Inventory; ESS = Epworth Sleepiness Scale; MEQ = Horne-Östberg Morningness-Eveningness Questionnaire; MCTQ = Munich Chronotype Questionnaire; PSQI = Pittsburg Sleep Quality Index; BMI = body mass index.

study protocol included two nights of partial sleep restriction (restriction to 6 h), we also excluded participants with usual sleep durations of <7 h and of >9 h (Aeschbach et al., 1996), to minimize a possible confounding effect of sleep duration (Table 1).

One week before the study, participants were requested to refrain from alcohol, caffeine, and chocolate intake in order to level out the impact of these consumption behaviors on sleep and the other investigated variables reported here (e.g., subjective sleepiness). They were also instructed to keep a regular sleep-wake schedule (bedtimes and wake times within ±30 min of self-selected target time) for 1 wk prior to each study segment. Compliance was verified by wrist actigraphy (Actiwatch L; Cambridge Neurotechnologies, Cambridge, UK) and self-reported sleep logs. Eighteen young healthy men (20–33 years old; mean ± SEM: 23.1 ± 0.8) who fulfilled all inclusion criteria were selected to participate in the study. One participant could not be included in the analysis because of poor quality of the EEG recordings and noncompliance during cognitive testing. The remaining 17 volunteers had the following light treatment order: 3 DL-BL-DsL, 3 BL-DsL-DL, 3 DsL-DL-BL, 3 DL-DsL-BL, 3 BL-DL-DsL, and 2 DsL-BL-DL; where BL is a blue monochromatic LED (light-emitting diode) light condition (100 lux at 470 nm for 20 min) starting 2 h after scheduled wake-up time, DsL is a dawn-simulating light starting 30 min before and ending 20 min after scheduled wake-up time (polychromatic light gradually increasing from 0 to 250 lux), and DL is a dim light (DL) condition for 2 h beginning upon scheduled wake time (<8 lux). Six participants were morning (59 to 86), nine intermediate (42 to 58), and two evening (16 to 41) chronotypes, according to the MEQ, whereas for the MCTQ, there were seven morning (0 to 3.99), four intermediate (4 to 4.99), and six evening (5 to 9.5) chronotypes. A comprehensive urine toxicological analysis for drug abuse was carried out prior to the study, along with an ophthalmologic examination in order to exclude volunteers with visual impairments (visual field, color vision, pupillary reflex).

The study was carried out during the winter season (January to March) in Basel, Switzerland, to minimize the effects of outdoor ambient light levels. The laboratory setup comprised a balanced crossover design with three segments (one control condition and two experimental conditions), separated by an at least 2-wk intervening period. Participants remained in individual windowless and sound-attenuated bedrooms under controlled 40 lux light condition, except for the first 2 h after wake-up during the morning light exposure (see below). No information on time-of-day was given. Each study segment lasted 48 h, comprising two sleep restriction (SR) nights (6 h) adjusted to each participant's habitual bedtime followed by two 18-h scheduled waking days (Figure 1A). The light protocol for each session consisted of a 2-h dim light (<8 lux) exposure after wake-up time followed by 40 lux until bedtime. The light treatment was administered after each sleep-restricted night, either with no additional light for the control condition, or with a blue light (BL; 2 h after wake-up, 20-min exposure of 100 lux of 470 nm; full width at half maximum [FWHM] 27 nm) with a photon density of 2.4E ± 18 photons/$m^2 \cdot s$ and a melanopic value of 4150 m-lux (goLITE BLU energy light; HF3330; Philips, Drachten, Netherlands) placed at 50 cm diagonally of the participant when he was sitting at the desk looking straight ahead (see Figure 1B for spectral composition), or with a DsL (polychromatic light gradually increasing from 0 to 250 lux during 30 min before wake-up time; the light remained around 250 lux for 20 min after wake-up time) placed near the bed at eye level (see Figure 1C for the time course of spectral composition). The illuminance, photon density, correlated color temperature and melanopic illuminance of the dawn simulation light, measured 45 cm from the device were as follows:

- 5 min after light onset: 1.2 lux, 1.9E ± 16/m^2 s, 1090 K, 0.2 m-lux
- 15 min after light onset: 13 lux, 1.4E ± 17/m^2 s, 1500 K, 7.5 m-lux
- 24 min after light onset: 78 lux, 7.1E ± 17/m^2 s, 2200 K, 120 m-lux
- 30 min after light onset: 250 lux, 2.4E ± 18/m^2 s, 2750 K, 620 m-lux

Subjective Assessment of Sleepiness, Well-being, and Mood

Subjective sleepiness was assessed every hour, using the Karolinska Sleepiness Scale (KSS) (Akerstedt et al., 1994). Subjective tension was measured using a 100-mm visual analog scale (VAS). Subjective well-being was assessed using a composite score calculated as follows: [VAS mood + (100 − VAS tension) + (100 − VAS physical comfort)]/3, according to Birchler-Pedross and colleagues (Birchler-Pedross et al., 2009). Subjective mood was investigated every 2 h on the Positive and Negative

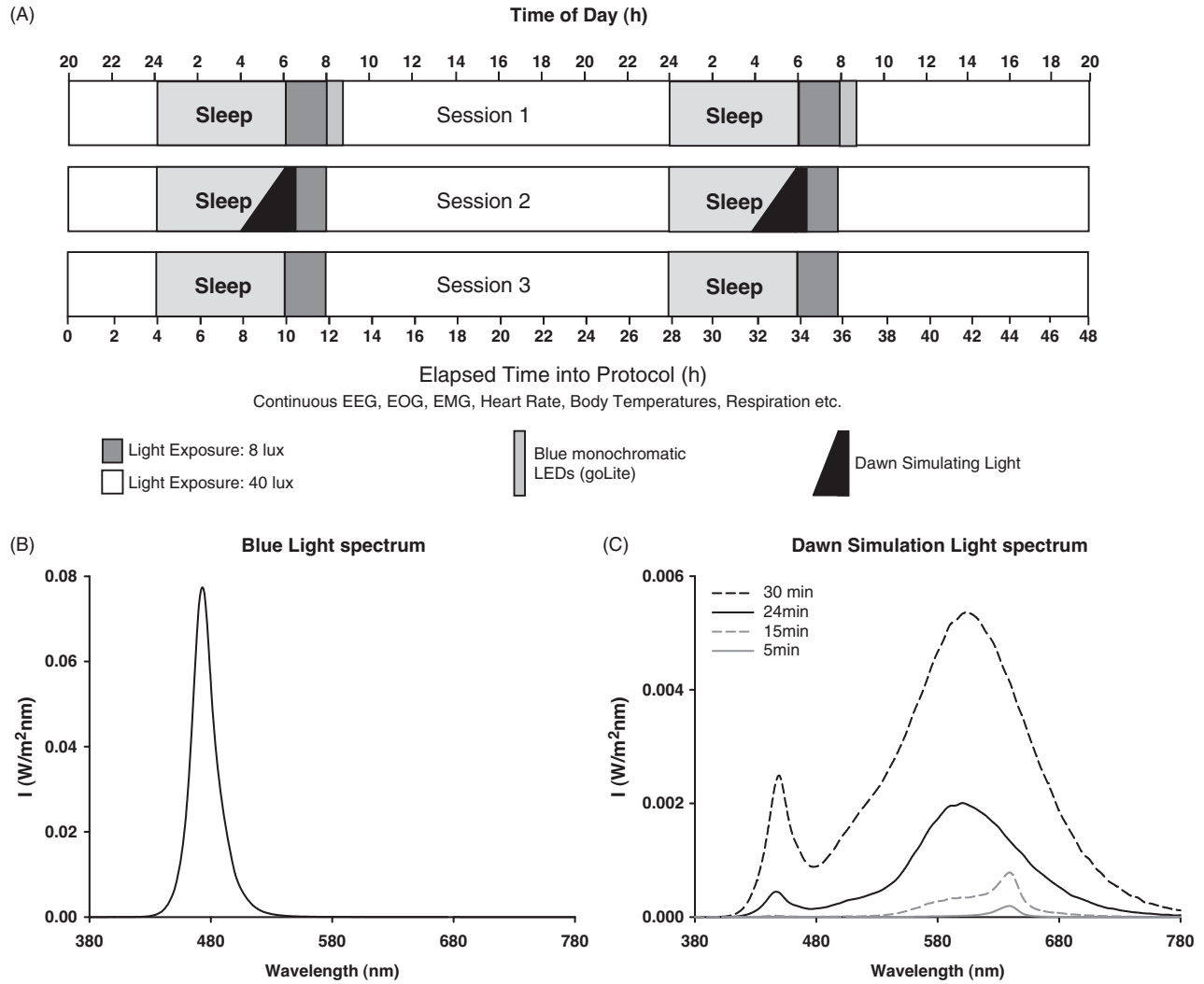

FIGURE 1. (A) Protocol design. Three conditions with different morning light exposures. Spectral composition (light wavelength by irradiance; W/m^2-nm) of the (A) blue light and the (B) dawn simulation light at 5 min (gray solid line), 15 min (gray dash line), 24 min (black solid line) and 30 min (black dash line).

Affect Scale (PANAS) (Watson et al., 1988). This questionnaire comprises two 10-item mood scales, and provides measures of positive affect (PA) and negative affect (NA) on a 5-point scale.

Cognitive Performance

Beginning 30 min after wake-up time, participants completed a 25-min test battery every 2 h. The battery included five cognitive tasks for sustained attention and executive functions: Sustained Attention to Response Task (SART; Robertson et al., 1997), Verbal 1-, 2-, and 3-back (N-Back1-2-3; Kubat-Silman et al., 2002), and Paced Visual Serial Addition Task (PVSAT; Feinstein et al., 1994). To quantify the magnitude of the light effects on global cognitive performance, a composite score was computed by normalizing the data for each test separately (i.e., SART, PVSAT, N-Back1-2-3) and averaging it to yield a composite score for each volunteer for each 2-h period according to Viola and colleagues (Viola et al., 2007).

Salivary Melatonin and Cortisol

Saliva samples were scheduled during wakefulness every 30 min during the first 4 h after wake-up time and followed by hourly intervals until bedtime, starting the first evening upon arrival at the laboratory. Salivary samples were immediately frozen and kept at −20 °C until the melatonin and cortisol assays were conducted. A direct double-antibody radioimmunoassay was used for the melatonin assay (validated by gas chromatography–mass spectroscopy with an analytical least detectable dose of 0.65 pm/mL; Bühlmann Laboratory, Schönenbuch, Switzerland; Weber et al., 1997). The minimum detectable dose of melatonin (analytical sensitivity) was determined to be 2 pg/mL.

Cortisol was measured by ALPCO (ALPCO Diagnostics, Salem, NH, USA), using a direct salivary enzyme-linked immunosorbent assay (ELISA) for quantitative determination of cortisol. The sensitivity was

TABLE 2. Analysis of variance for different variables for the time course of the study.

	Analysis of variance		
Variable	Light	Time of day	Light × Time of day
Sleepiness	$F_{2,658} = 4.70,\ p < 0.01$	$F_{14,658} = 14.40,\ p < 0.0001$	$F_{28,658} = 0.46,\ p = 0.9927$
Well-being	$F_{2,658} = 12.00,\ p < 0.0001$	$F_{14,658} = 6.20,\ p < 0.0001$	$F_{28,658} = 0.47,\ p = 0.9922$
Tension	$F_{2,658} = 13.20,\ p < 0.0001$	$F_{14,658} = 3.40,\ p < 0.0001$	$F_{28,658} = 0.53,\ p = 0.9786$
Positive mood	$F_{2,702} = 3.17,\ p = 0.0426$	$F_{14,702} = 8.33,\ p < 0.0001$	$F_{28,702} = 0.96,\ p = 0.5291$
Negative mood	$F_{2,702} = 8.21,\ p = 0.0003$	$F_{14,702} = 0.44,\ p = 0.9617$	$F_{28,702} = 0.42,\ p = 0.9965$
Cognitive performance	$F_{2,658} = 10.31,\ p < 0.0001$	$F_{14,658} = 0.32,\ p = 0.9920$	$F_{28,658} = 0.40,\ p = 0.9978$

1.0 ng/mL and intra-assay coefficient of variances amounts to 10.3% for baseline values 6.6 ng/mL.

Statistical Analysis

For all analysis, the statistical package SAS (version 9.1; SAS Institute, Cary, NC, USA) was used. Statistical analyses were carried out for each variable (subjective sleepiness, subjective well-being, positive and negative affects, and cognitive performance) separately with the mixed-model analysis of variance for repeated measures (PROC MIXED), with within factors ''light condition'' (dim light [DL] versus blue light [BL] versus dawn simulation light [DsL]) and ''time-of-day'' (all assessed time points). The rationale for this approach was that time-of-day was deemed as a continuum, and thus a better form to illustrate the temporal dynamics of all our dependent variables. The time course of the melatonin profiles were analyzed for each day (SR1 and SR2) separately, since melatonin onsets were only available for the baseline evening and in the evening after SR1. Cortisol analysis was also done separately for SR1 and SR2, since we intended to analyze the wake-up response after both sleep restriction nights. Contrasts were assessed with the LSMEANS statement, and degrees of freedom were corrected with the Kenward-Rogers contrasts. The Wilcoxon-Mann-Whitney test was used for post hoc comparisons, since not all data reached the criterion for a normal distribution. Alpha adjustment for multiple comparisons was applied according to Curran-Everett (Curran-Everett, 2000).

For the analyses of the dim light melatonin onset (DLMO) following exposure to either DL, BL, or DsL, data were *z*-scored to provide a normalized comparison of amplitudes across each individual (Zeitzer et al., 1999). The individual *z*-score adjustment provides a mean at 0 with a variation of 1. For each melatonin profile, we derived a DLMO using a fixed threshold of 0. The DLMO was defined as the time when melatonin levels hit and exceeded the threshold. The time the melatonin levels crossed the threshold was determined by linear interpolation between the points immediately below and above the threshold on the day following exposure to either BL or DsL relative to melatonin onset on the day prior to light exposure (baseline levels of melatonin under dim light conditions) (Zeitzer et al., 1999).

RESULTS

Subjective Assessment of Sleepiness, Well-being, and Mood

With respect to subjective sleepiness, we observed a significant main effect of ''light condition'' and ''time-of-day'' (Table 2). Analysis revealed no significant influence of light exposition on subjective sleepiness after the first sleep restriction (SR). However, after the second SR, participants felt subjectively sleepier following BL exposure compared with the DsL and DL conditions (Figure 2, first panel). Post hoc analysis revealed a significant difference between the DsL and the DL exposure at 10 h of elapsed time awake (ca. 16:00 h the afternoon) after the second night of sleep restriction and between the BL and the DL exposure at 4 h of elapsed time awake (ca. 10 h the morning) after the second night of sleep restriction (Wilcoxon non-parametric test).

Concerning well-being, we observed a significant main effect for the factors ''light condition'' and ''time-of-day'' (Table 2). Furthermore, considering the light effect, analyses revealed that the participants felt generally better during the entire study after a DsL exposure compared to a BL or a DL exposure. Compared with the BL exposure, well-being after the DsL improved during approximately 7 h after the first SR night. After BL exposure, well-being levels were maintained stable compared with DL condition. After the second SR night, the level of well-being was likewise increased after a DsL exposure throughout all the day. Post hoc analysis revealed a significant difference between the DsL and the DL exposure at 10 and 12 h of elapsed time awake (ca. 16:00 and 18:00 h the afternoon) after the second night of sleep restriction (Wilcoxon non-parametric test) (Figure 2, second panel).

A similar profile was observed with respect to subjective tension (main effect of ''light condition'' and ''time-of-day''; Table 2). Subjective tension was lower after a DsL exposure compared with BL or DL exposure across all the experiment. Post hoc analysis revealed a significant difference between the DsL and the DL exposure at 6, 10, and 12 h of elapsed time awake (ca. 12:00, 16:00 and 18:00 h the afternoon) after the second night of sleep restriction (Wilcoxon non-parametric test) (Figure 2, third panel).

Concerning the mood scales, we observed significant effects of ''light condition'' and ''time-of-day'' when

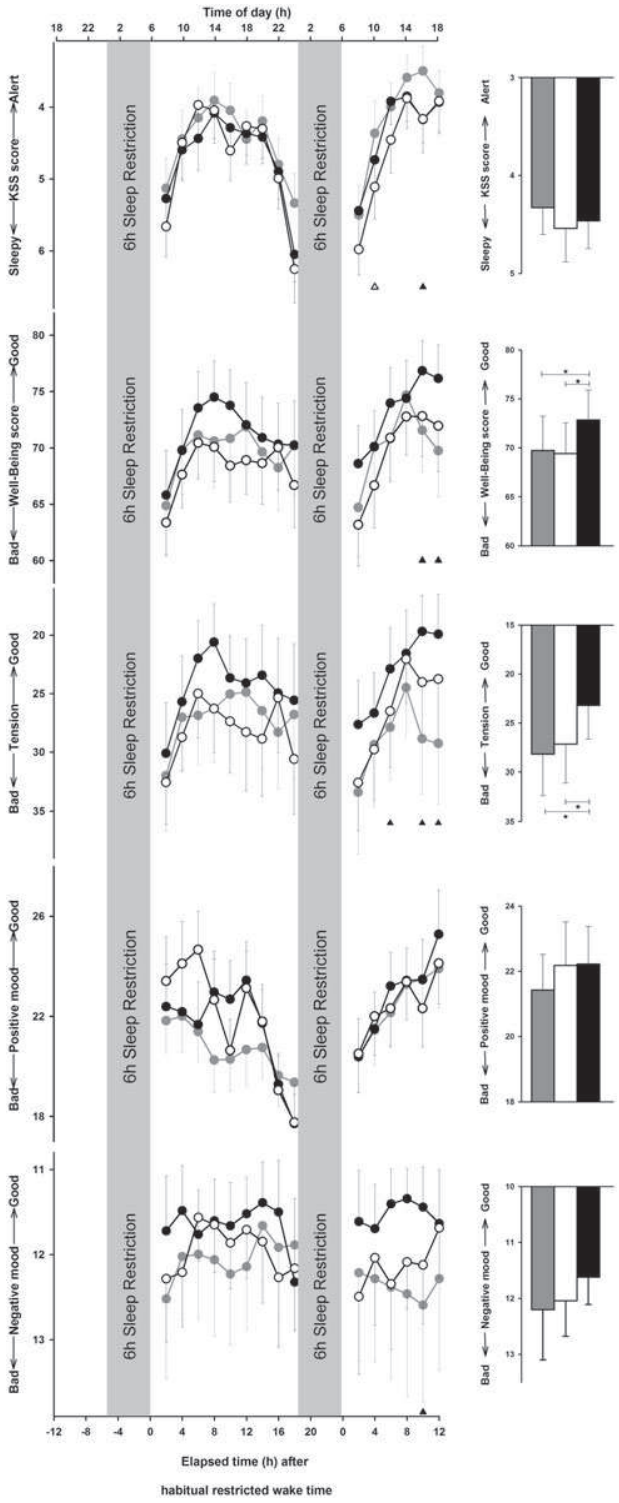

FIGURE 2. Time course (left panel) and mean of all the time points (right panel) of (top to bottom) subjective sleepiness, subjective well-being, tension, positive mood, and negative mood in 17 participants under dim light (dark gray lines), monochromatic blue LEDs (black lines with white circles), or dawn simulation light (black lines with black circles). Data are plotted as a mean for each 2-h bin relative to elapsed time (h) after wake time, and the error bars represent the standard error of the mean. Post hoc comparisons were carried out using the Wilcoxon-Mann-Whitney test between the DsL and the DL (▲, $p<0.05$) and between the BL and the DL (Δ, $p<0.05$).

looking at the overall time course. DsL and BL exposures helped maintaining mood after the first SR night, whereas under the dim light condition, positive mood was significantly lower. After the second SR night, positive mood was equal across all light settings (Figure 2, fourth panel). However, the post hoc analysis did not reveal significant light effects.

For the negative mood scale, only a main effect of ''light condition'' was found. A reverse pattern was also observed: although the light condition did not affect negative mood after the first sleep restriction night, DsL was able to decrease negative mood over the day following the second sleep restriction night. Post hoc analysis revealed a significant difference between the DsL and the DL exposure at 10 h of elapsed time awake (ca. 16:00 h the afternoon) after the second night of sleep restriction (Wilcoxon non-parametric test) (Figure 2, fifth panel).

Cognitive Performance

Analysis of the composite score of cognitive performance revealed a significant main effect of ''light condition'' when looking at the overall time course. Nevertheless, analysis did not reveal a general significant effect concerning the light treatment. Following the first sleep restriction night, cognitive performance was significantly better following morning DsL exposure compared with morning BL exposure, in which performance did not differ compared to DL. After the second SR night, these differences were no longer significant between DsL and DL. Interestingly, cognitive performance started on a higher level the day following the second SR compared to the level before this SR night under the latter light conditions, whereas levels remained similar for the blue light condition until the end of the protocol. Post hoc analysis revealed a significant difference between the DsL and the DL exposure at 16 h of elapsed time awake (ca. 22:00 h the afternoon) after the first night of sleep restriction (Wilcoxon non-parametric test) (Figure 3).

Salivary Melatonin

During the baseline evening, before the first SR and light intervention, melatonin levels were equal across all conditions. However, analysis of the melatonin profile during the first evening after morning light exposure yielded a significant main effect of ''light condition'' ($F_{2,280}=9.3$, $p=0.0001$) and ''time-of-day'' ($F_{6,280}=62.7$, $p<0.0001$), as well as an interaction ''light condition'' versus ''time-of-day'' ($F_{10,280}=2.0$, $p<0.04$). Although melatonin levels were not affected by the DsL, neither after the first, nor after the second SR; morning BL exposure elicited a phase advance in salivary melatonin. Melatonin secretion increased earlier after a BL exposure than after a DsL or DL exposure (Figure 4A). Congruently, we found a main effect of ''light condition'' ($F_{2,27.4}=5.4$, $p=0.01$) for the DLMO, which was significantly earlier after morning BL (21:20 h ± 19 min)

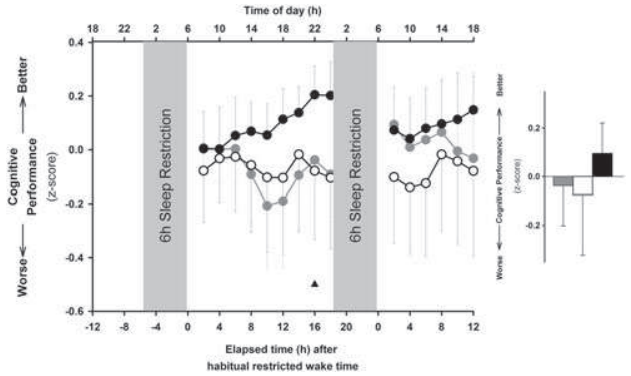

FIGURE 3. Time course (left panel) and mean of all the time points (right panel) of the composite of cognitive performance in 17 participants under dim light (dark gray lines), monochromatic blue LEDs (black lines with white circles), or dawn simulation light (black lines with black circles). Data are plotted as a mean for each 2-h bin relative to elapsed time (h) after wake time, and the error bars represent the standard error of the mean. Post hoc comparisons were carried out using the Wilcoxon-Mann-Whitney test between the DsL and the DL (▲, $p<0.05$) and between the BL and the DL (Δ, $p<0.05$).

exposure compared to DL (21:50 h ± 23 min; $p=0.003$) and DsL (21:38 h ± 17 min; $p=0.05$) exposure.

Salivary Cortisol

Comparable to melatonin profile, cortisol levels were similar across sessions on the first evening, before intervening SR and light application. After light exposure and SR, a main effect of ''light condition'' was observed, irrespective of whether the morning after the first ($F_{2,363}=3.3$, $p=0.0383$) or second ($F_{2,381}=3.5$, $p=0.0317$) SR night was considered. Compared to the DL condition, cortisol levels decreased during the first evening after 13 to 16 h of elapsed time awake (i.e., corresponding time-of-day: 18:00 h to 22:00 h) after a morning BL exposure but not after a DsL exposure ($F_{2,270}=8.9$, $p=0.0002$). Additionally, during the first hour since awakening, a significant increase in cortisol levels upon wake-up with the DsL was observed during both mornings after SR (mean ± SEM: DL = 20.35 ± 1.43 ng/mL; BL = 22.96 ± 1.49 ng/mL; DsL = 31.99 ± 2.13 ng/mL) compared to the two other conditions ($F_{2,32}=15.65$, $p<0.0001$) (Figure 4B).

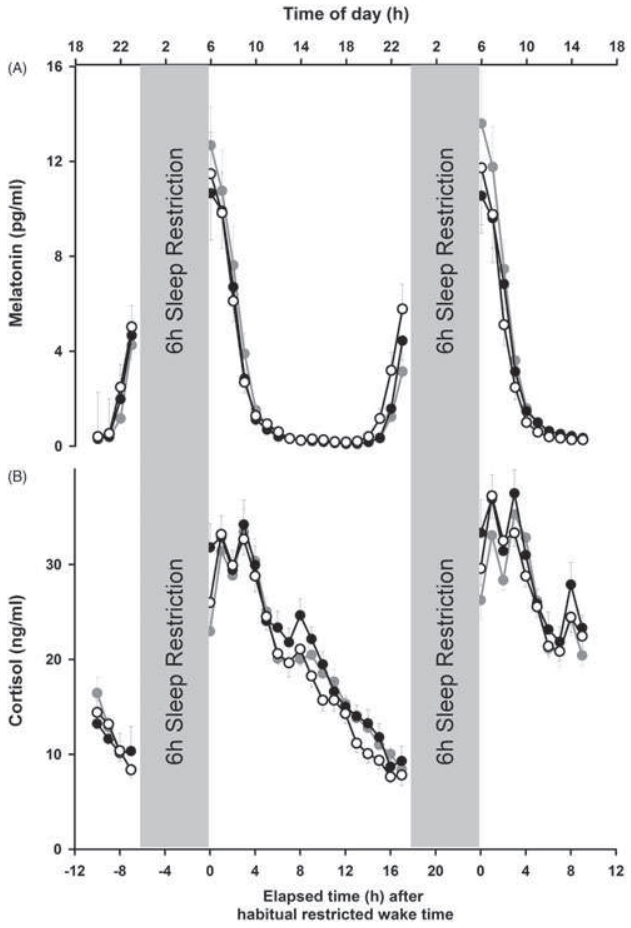

FIGURE 4. Time course of salivary (A) melatonin and (B) cortisol profiles in 17 participants under dim light (dark gray lines), monochromatic blue LEDs (black lines with white circles), or dawn simulation light (black lines with black circles). Data are plotted as a mean for each 2-h bin relative to elapsed time (h) after wake time, and the error bars represent the standard error of the mean.

DISCUSSION

Here we investigated whether the exposure to artificial light sources, differing in their dynamics and spectral sensitivity, can facilitate the waking-up process and allow the improvement of subjective parameters of well-being, sleepiness, and tension, as well as cognitive performance throughout a sustained period of wakefulness, following sleep restriction. Our data suggest that morning exposure to dawn simulation light can significantly improve subjective perception of well-being, mood, and tension, as well as cognitive performance. Importantly, this effect can persist up to 18 h after light exposure. In parallel, dawn light simulation did not change the circadian phase of cortisol and melatonin profiles, in contrast to exposure to blue monochromatic light-emitting diodes (LEDs). In other words, although the light effects on classical markers of circadian phase showed maximal sensitivity to short-wavelength light exposure (blue monochromatic LEDs), the sustained effects on subjective well-being, mood, tension, and cognitive performance were mostly driven by the exposure to a broadband polychromatic light source simulating dawn.

The strengths of this study are the strictly controlled laboratory conditions and the selection criteria of the volunteers (sleep-wake times were similar for all participants), which allowed us to carefully quantify and analyze the effects of dawn simulation light and blue monochromatic light in contrast to a dim light condition, and to thus conclude that our light-induced effects were not driven exclusively by prior differences in circadian phase and sleep pressure levels.

Our data are in line with previous observations indicating that 30 min of artificial dawn light exposure in the morning hours improves subjective well-being during the time window of sleep inertia (Gimenez et al., 2010). Similarly, we found that light exposure around wake-up time counteracted the detrimental effects of sleep inertia, resulting in higher subjective well-being, but also in more positive (respectively less negative) mood as assessed by a validated affect scale (PANAS). Importantly, our data show for the first time that these effects are sustained over a whole waking day after one sleep-restricted night (for mood measures) and are even still operational after two nights of partial sleep restriction for subjective well-being and tension.

Beneficial effects of light on mood may be mediated through long-term circadian effects (Avery et al., 2001; Lewy et al., 1987). Another possible neuroanatomical modulator for these effects is the amygdala, a key component of the limbic system, which encompasses brain areas related to emotion processing, with direct projections from melanopsin-containing intrinsic photosensitive retinal ganglion cells (ipRGCs), and is acutely affected by light exposure (Vandewalle et al., 2010).

Our data suggest that dawn simulation light could induce facilitation of the wake-up process and allows a sustained beneficial effect throughout the entire waking day. Interestingly, the observed increase of subjective well-being, tension, and mood was associated with higher cortisol levels after wake-up with the dawn simulation light, in comparison with dim light and monochromatic blue LED exposure, which was most likely applied too late to induce any cortisol response. Light after wake-up (Scheer & Buijs, 1999), and especially dawn simulation light (Thorn et al., 2004), has previously been reported to affect cortisol levels upon awakening. Furthermore, bright light seems to trigger maximal effects on cortisol secretion when applied during the upward portion of cortisol secretion, i.e., in the early morning hours, close to wake-up time (Jung et al., 2010). It may be assumed that these increased cortisol levels upon wake-up reflect a light-induced stress response. However, we observed that our volunteers felt subjectively more relaxed after DsL exposure as compared to BL and DL. Alternatively, and in line with what we observed at the subjective level, DsL before and after wake-up could facilitate the wake-up process per se and positively affect the process of sleep inertia by increased cortisol levels immediately after wake-up. Such an effect might be mediated by the suprachiasmatic nuclei (SCN), which have direct multisynaptic neural pathways to the adrenal cortex (Buijs et al., 1999).

Dawn simulation light increased cognitive performance levels over the first day after SR. This beneficial effect was no longer maintained after the second SR night. It may thus be assumed that artificial dawn simulation light is beneficial for the maintenance of cognitive performance, but only if homeostatic sleep pressure, as challenged by SR, is not sufficiently high to be ''unresponsive'' to light. Recent functional magnetic resonance imaging (fMRI) studies propose a cerebral network underlying beneficial non-image-forming effects of light on cognition (Vandewalle et al., 2009a). It is suggested that the light irradiance signal impinges onto the SCN, indirectly communicating with the brainstem locus coeruleus, which in turn presents thalamic and cortical connections allowing modulation over widespread cortical networks implicated in successful cognitive performance (Vandewalle et al., 2009b). However, little is known about the magnitude, dynamics, and regional brain distribution of such non-image-forming effects and how properties, such as dose, duration, intensity, and for instance different light dynamics impact on the above mentioned networks (Chellappa et al., 2011a). Subcortical regions are thought to be more promptly activated and display short-lasting responses to light, whereas the long-lasting and widespread cortical task-related brain responses appear when light exposure is longer and at a higher intensity (Perrin et al., 2004). It may be speculated that the duration of light exposure, here indexed by 30 min of gradually increasing polychromatic light exposure (dawn simulation light) followed by 20 min of moderate light exposure (light duration of 50 min), results in such long-lasting optimal cognitive performance across the day.

Spectral sensitivity of non-image-forming effects of light on circadian physiology has repeatedly been shown to be highest in the short-wavelength range of the visible light spectrum (Brainard et al., 2001; Gooley et al., 2010). In our study, we observed that a 20-min exposure to monochromatic blue LEDs 2 h after wake-up did not affect subjective sleepiness, tension, and cognitive performance compared to a dim light condition. However, we did not have a control light condition at equal time-of-day with the same duration as comparison. We also did not measure during the blue light exposure but only 40 min later for the KSS and 10 min later for mood and cognition. Moreover, most of the studies reporting specific spectral sensitivity of blue light on alertness in humans administered light either during nighttime or the evening hours (Cajochen, 2007; Chellappa et al., 2011a), except for the fMRI study (Vandewalle et al., 2006).

Concomitant to the absence of effects at the subjective and cognitive levels after BL exposure as compared with the DL control condition, we observed a significant phase advance in the circadian phase markers of melatonin and cortisol after morning blue LED exposure. Our results are in line with previously observed phase advances for melatonin after 6.5 h bright light exposure centered after the core body temperature nadir (Khalsa et al., 2003). Exposure to intermittent blue LED light (three 30-min pulses over 2 h) over 3 days induced melatonin phase shifts, such that the phase advances extend later in the day and the phase delays start earlier

relative to white light (Revell et al., 2012). Very recently, a phase response curve (PRC) for short-wavelength (monochromatic blue 480 nm) light was constructed to assess DLMO phase shifts (Ruger et al., 2013). Exposure to 6.5 h of 480 nm light indicated fitted maximum delays and advances of −2.6 and 1.3 h, respectively. Furthermore, the 6.5 h of 480 nm, 11.2 lux light PRC resulted in approximately 75% of the response of the 6.7 h of 10 000 lux white light PRC. This capacity for blue light (during the phase-advancing portion of the human PRC) to significantly advance DLMO may thus explain our earlier melatonin onset following a 20-min morning light exposure to monochromatic blue LED relative to DSL and DL. One likely explanation is the higher irradiance and melanopic values in the short wavelength, since the mechanisms involved in melatonin suppression are mostly sensitive to this wavelength (Brainard et al., 2001, 2008). Blue light impinges onto the non-image-forming pathway, involving melanopsin-containing intrinsic photosensitive retinal ganglion cells (ipRGCs), which then modulates responses in the ventrolateral preoptic nucleus (VLPO) and the SCN via a specialized non-image-forming retinohypothalamic tract with direct neuronal connections to the SCN (Tsai et al., 2009). Given that the SCN is directly involved in the circadian timing system, with direct neuronal projections to the pineal gland (central site for melatonin production), nocturnal melatonin secretion would then phase advance, as would be predicted by the classical phase response curve of light to the circadian system (Khalsa et al., 2003; Minors et al., 1991).

Nevertheless, the magnitude of which our data can be extrapolated to real-life settings should be viewed with caution, since under those conditions, other concomitant effects such as social constraint, exposure to outdoor light, and different types of artificial lighting, may mask, minimize, or perhaps even enhance the effects of our current results. Future studies under real-life settings may be required to probe the extent to which morning light devices may impact on mood and cognitive performance, particularly on a long-term perspective.

CONCLUSION

Our data indicate that exposure to artificial morning dawn simulation light improves subjective perception of well-being and mood, as well as cognitive performance, under conditions of mild sleep restriction. Concomitantly, it did not result in phase advances of cortisol and melatonin profiles, as induced by the blue light, thus resulting in a minimal impact on the circadian timing system. In a broader context, these light conditions may provide an effective rationale for enhancing performance and mood in individuals who experience conditions of mild sleep restriction.

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DECLARATION OF INTEREST

This research was supported by Philips Consumer Lifestyle, Drachten, The Netherlands.

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IV- Morning light effect in young study volunteers

1/ Circadian physiology

Dawn Simulation Light: A Potential Cardiac Events Protector.

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Original Article

Dawn simulation light: a potential cardiac events protector

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ABSTRACT

Objective/Background: Major cardiovascular events frequently increase in the morning due to abrupt changes in the sympatho-vagal cardiac control during the transition from sleep to wakefulness. These neural changes are translated into stepwise increases in cardiac functions, resulting in a potential cardiovascular stress. Here, we explored whether light can "optimize" heart rate and its neural control, by actively promoting a less steep transition from sleep to wakefulness, thus minimizing morning cardiovascular vulnerability.
Methods: Seventeen healthy young men were awakened 2-hours before their habitual wake-time. In a counterbalanced within-subject design, we applied a control condition (darkness during sleep and dim light during wakefulness) or dawn-simulation-light (DSL) starting 30-minutes before and ending 30-minutes after scheduled wake-up time.
Results: Our data reveal a significantly gradient reduction in heart rate during the transition from sleep to wakefulness, when applying DSL as compared to a control condition. Likewise, cardiac sympatho-vagal control smoothly increased throughout the 30-min sleep episode preceding scheduled wake-up under DSL and remained stable for the first 30-min of wakefulness. Interestingly, these effects were mostly driven by changes in the parasympathetic cardiac control.
Conclusions: Our data demonstrate for the first time that a non-invasive strategy, as light exposure surrounding the wake-up process, can significantly reduce the deleterious sleep-to-wake evoked cardiac modulation in healthy young men awakened under conditions of increased sleep pressure. A translational approach of this light exposure, which closely resembles natural lighting conditions in the morning, may therefore act as a potential protector for cardiac vulnerability in the critical morning hours.

1. Introduction

Key cardiovascular events are increasingly more intense in the morning hours between 06:00 and 12:00 h [1–3], although they may also occur in the evening (between 18:01 h and midnight) [4], and are associated to higher blood pressure, heart rate (HR), platelet aggregation, vascular resistance and so forth [5]. In particular, sleep–wake transitions in the morning elicit high shifts toward sympathetic activation, in comparison to the remainder of the day, suggesting a key role in increasing cardiac vulnerability after awakening [6,7]. This "morning bias" in major cardiovascular regulatory mechanisms is a salient feature of ischemic diseases, such as brain vascular disease, cerebral infarction, angina and myocardial infarction [5]. Physiological underpinnings for possible adverse cardiovascular events encompass abrupt changes in the autonomic nervous control of the cardiovascular system "around the clock" [8]. The circadian clock impacts on both endothelial and muscle cells [9], as indexed by the 24-h daily fluctuation in nearly 300 genes in the aorta *alone*, most of which directly involved in vascular function [10]. In mouse models deficient for specific "clock genes," blood pressure and heart rate show abnormal timing and amplitude [11]. Conversely, clinical findings also suggest a small 1.28-fold greater incidence of acute MI in a wide window (6 am to noon) compared to other times of day [2], bimodal peaks in morning and evening hours [4], and stress-related contributors to adverse cardiovascular events [3]. Thus, it still remains a matter of debate whether circadian factors play a key role on the onset of long-term cardiovascular events. Nevertheless, a dysfunction of the circadian clock may be one possible risk factor for potential cardiovascular diseases, contributing to some extent to the morning increased rates of HR and heart rate variability (HRV). In this context, strategies allowing for the "optimization" of internal biological

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rhythms regulating cardiovascular events may provide a means to counteract possible adverse events. Quite surprisingly, no non-invasive strategies are known to date.

The present study investigated whether light can "optimize" heart rate and its neural control, by actively promoting a less steep transition from sleep to wakefulness, thus minimizing morning cardiovascular vulnerability. We hypothesized that a "naturalistic" dawn simulation light (DSL) surrounding the wake-up time would result in a smoother increase heart rate and heart rate variability during the transition from sleep to wakefulness, as compared to a control condition. Likewise, we hypothesized that cardiac sympatho-vagal control would smoothly increase during the transition from sleep to wakefulness, as light may minimize the deleterious sleep-to-wake evoked increases in cardiac modulation in the early hours of the morning.

2. Materials and methods

2.1. Participants

Eighteen healthy young men (age range, 20–33 years; mean, 23.1 ± 0.8 years [SD]) participated in a laboratory study on impact of polychromatic light on cognitive performance and sleep–wake regulation [12]. All participants were nonsmokers, drugs and medication free (drug screening prior to the study onset), and devoid of medical, psychiatric, and sleep disorders. Clinical status of all participants was assessed by questionnaires, physical examination, and a polysomnographically recorded adaptation night. This night served as screening night for potential periodic limb movements and sleep apnea, as well as for optimal sleep quality (sleep efficiency >85%). During the baseline week preceding the study, participants were instructed to keep their individual bed- and wake-time within a self-selected range of ±30 min and to sleep for 8 h, as assessed by a wrist activity monitor (Cambridge Neurotechnologies) and sleep logs. Adherence to this individually timed sleep–wake schedule was checked prior to the beginning of the study. Participants were requested to abstain from excessive caffeine and alcohol consumption. The study protocol, the screening questionnaires, and consent form were approved by the Ethical Committee of Basel, Switzerland and were in agreement of the Declaration of Helsinki. All study participants gave their written informed consent.

2.2. Protocol

The study was carried out during the winter season (January to March) in Basel, Switzerland, and comprised two segments in a balanced cross-over design, separated by at least 1-week intervening period. No order effects were observed due to this cross-over design. Participants remained in individual bedrooms with no information about time of day. All rooms were completely dark, without windows. The experiment lasted 48 h, including 2 days and two sleep restriction nights (6 h) following the habitual subject sleep time. The rationale for including a study protocol with two sleep restriction nights was due to two major reasons: (1) chronic sleep restriction (CSR) is increasingly usual in contemporary society, negatively impacting on numerous aspects of human physiology [13]. However, CSR impact on cardiac physiology is virtually unknown; (2) light dynamically promotes increased alertness and cognitive performance, and has been shown to ameliorate the deleterious effects of CSR on subjective alertness and performance [12]. However, it remains completely unknown if light can act as an adjuvant on minimizing potentially deleterious cardiovascular events, under increased sleep pressure. During the day, participants were exposed to dim light (<8 lux) during 2 h after wake-up and to 40 lux until they went to bed. Blood pressure measurements were performed after wake-up times on both days of the study protocol, and no significant differences were observed between DSL and control conditions. The light treatment was administered after the sleep restriction night either with no additional light for the control condition or with a DSL. Polychromatic DSL light gradually increasing from 0 to 250 lux during 30 minutes before wake-up time; the light remained around 250 lux for 20 minutes after wake-up time, placed near the bed at eye level. DSL illuminance, photon density, and correlated color temperature, at 45 cm from the device, were: (1) 5 min after light onset: 1.2 lux, 1.9E$\pm$16/m2 s, 1090 K; (2) 15 min after light onset: 13 lux, 1.4E$\pm$17/m2 s, 1500 K; (3) 30 min after light onset: 250 lux, 2.4E$\pm$18/m2 s, 2750 K. The control "wake-up technique" (non-DSL condition) was with a technician's voice.

2.3. Salivary cortisol

Saliva cortisol samples were scheduled during wakefulness every 30 min during the first 4 h after wake-up time and followed by hourly intervals thereof. Samples were frozen and kept at –20 °C until the cortisol assays were conducted. Cortisol was measured by ALPCO (ALPCO Diagnostics, Salem, NH, USA), using a direct salivary enzyme-linked immunosorbent assay (ELISA) for quantitative determination of cortisol. The sensitivity was 1.0 ng/mL and intra-assay coefficient of variances amounts to 10.3% for baseline values 6.6 ng/mL.

2.4. Electrocardiographic (ECG) recordings and analysis

A two-derivation ECG system was recorded throughout the laboratory study. R–R intervals, ie, time length between the R peaks of consecutive QRS complexes, were calculated, and all traces were visually checked for artifacts by an investigator. The R wave peak detection and R–R signal were analyzed by HeartScope software (AMPS, Inc, NY, USA). Occasional ectopic beats were identified and replaced with interpolated R–R interval data. All data acquisition and post-acquisition analyses were carried out in accordance with established standards, including those put forth by the Task Force on HRV Interpretation [14]. To avoid excluding large sections of the recording contaminated by movement artifacts during wakefulness, we used a sampling period of 2.5 min for HRV estimation [15], in accordance with the recommendations of the Task Force on HRV Interpretation [14]. Power densities in the low-frequency (LF) band (0.04–0.15 Hz) and in the high-frequency (HF) band (0.15–0.50 Hz) were calculated for each 2.5-min segment using autoregressive algorithms. Moreover, the LF-to-(LF + HF) ratio [LF/(LF + HF) ratio] was used as an index of sympatho-vagal balance. The indexes selected are those most commonly used in the analysis of HRV [16,17]. Furthermore, we also performed symbolic analyses to quantify different aspects of cardiac control related to the organization of different autonomic subsystems. Symbolic analysis is a non-linear method based on the conversion of the series into a sequence of symbols [17–19]. The full dynamic of the series (the min–max range) is spread over six bins, each of which is identified by a number (symbol) from 0 to 5. Original values inside each bin are substituted by the symbol defining the specific bin, thus obtaining a symbolic series. The symbolic series is converted into a series of patterns of three symbols. Four different families of patterns can be identified [17–19]: 0V (patterns with no variation, all symbols are equal), 1V (patterns with one variation, two consecutive symbols are equal and the remaining one is different), 2LV (patterns with two like variations, the second and the third symbol change with respect to the previous one and the changes have the same sign), and 2UV (patterns with two unlike variations, the second and the third symbol change with respect to the previous one and the changes have opposite sign) [19]. This method has been applied to evaluate cardiac autonomic control from HRV [18]. It has been demonstrated that 0V% is a marker of

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sympathetic modulation of HR, while 2UV% is a marker of vagal modulation [17].

2.5. Statistical analysis

All statistical analyses were performed with SAS version 9.1. Mixed-model ANOVA for repeated measures (PROC MIXED) was used for the repeated measures analyses of within-factors 'light settings' (DSL and dim light) and 'time'. Contrasts were assessed with the LSMEANS statement. All *P* values were based on Kenward–Roger's corrected degrees of freedom (29).

3. Results and discussion

During the transition from sleep to wakefulness, salivary cortisol levels were significantly higher after 30 min of wakefulness under the "naturalistic" DSL source relative to the control condition (Fig. 1A). However, no significant time effects were observed between the two conditions thereof.

The time series of consecutive R–R intervals (heart rate; beats per minute) from sleep-to-wake transition, as indexed from continuous ECG recordings, exhibited with the control condition evoked a HR increases from 63.6 ± 2.5 to 89.7 ± 3.7 bpm. Conversely, the DSL condition resulted in HR increases from 65.5 ± 4.8 to 78.4 ± 5.0, thus indicating a significant gradient reduction ($p < 0.05$) (Fig. 1B). To better illustrate the dynamics of this less steep light effect on heart rate, data were collapsed in two time bins, ranging from "baseline period" (–60 to –30 min before wake-up time), centered on wake-up time (–30 to 0 min) and immediately after wake-up time (0–30 min after) (Fig. 1C). No differences were observed during the baseline period between light conditions (DSL and control condition: darkness). Thus, all participants were under a similar cardiac state prior to the experimental light setting. During the period centered on wake-up time, heart rate significantly increased when individuals were exposed to the DSL source, while it remained constant for the control condition (darkness) ($p < 0.05$). Interestingly, in the period immediately after wake-up time, relative to the time preceding it, the increase in heart rate was significantly lower under DSL as compared to the control condition (Dim light <8 lux) ($p < 0.05$). These less steep light changes in the dynamics of heart rate were mirrored by specific variations in cardiac sympatho-vagal modulation, as indexed by classical measures of heart rate variability, such as the ratio between power density of low-frequency (0.04–0.15 Hz) and high-frequency bands (0.15–0.50 Hz) (LF/(LF + HF)). Similar to instantaneous heart rate, cardiac sympatho-vagal modulation smoothly increased in the 30-min sleep episode preceding wake-up *only* when individuals were exposed to a "naturalistic" dawn simulation light, which remained stable during the subsequent 30 minutes of wakefulness after scheduled wake-time ($p < 0.05$).

Heart rate variability comprises a powerful tool largely used in physiological and pathological conditions, as a window over cardiovascular control mechanisms [20,21]. To access different aspects of cardiac control related to the organization of different autonomic subsystems, we used a novel symbolic analysis method [17,22]. By means of this non-linear method, we indirectly measured the impact of light onto specific autonomic subsystems, as sympathetic and parasympathetic cardiac control. These are modulatory reacting systems that control heart rate with different latent periods and time courses, such that sympathetic effects on heart rate are much slower than parasympathetic effects [18]. We observe that DSL significantly impacts mostly on the parasympathetic cardiac activity (Fig. 2A and B). During the transition from sleep to wakefulness, sympathetic cardiac predominance is kept relatively stable between both experimental light settings (Fig. 2A). Conversely, parasympathetic cardiac activity is maintained

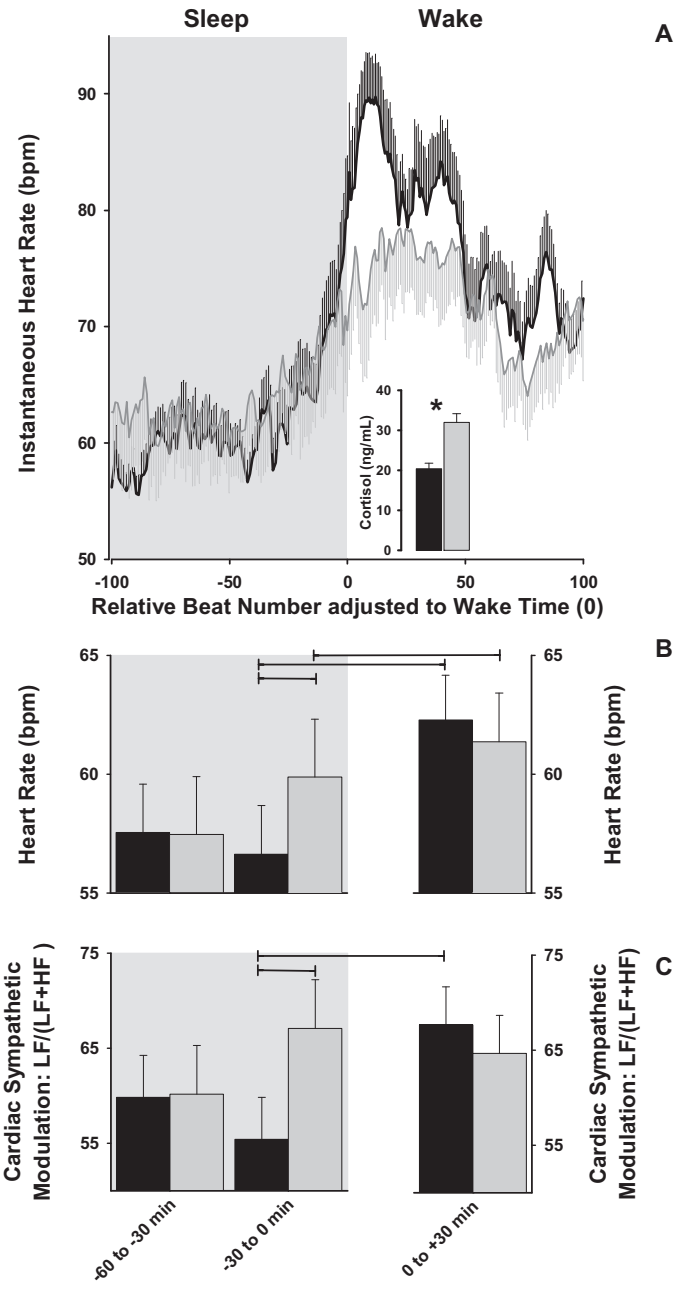

Fig. 1. Cardiac modulation surrounding the sleep–wake transition: Increase in instantaneous heart rate (A), heart rate (B) and cardiac sympathetic [LF/(LF + HF) ratio] (C) variation during the transition from sleep to wakefulness under dim light (black) and dawn simulation light (gray). Data in Band C were averaged for 30 min bin, separately during sleep without light, gradual light increase and after wake time (0). Error bars represent SEs. Horizontal bar characterize the significant difference between conditions ($p < 0.05$).

stable *only* when participants are exposed to DSL, while a drastic decrease is observed under dim light ($p < 0.05$) (Fig. 2B). Therefore, dawn light exposure may minimize the sharp decrease in parasympathetic cardiac control, allowing for heart rate "stability", during the critical transition of sleep to wakefulness. Collectively, the data show that "naturalistic" light exposure centered during wake-up time potentially minimizes abrupt cardiovascular events, as indexed by less steep transitions in instantaneous heart rate, sympatho-vagal balance and in specific cardiac autonomic systems.

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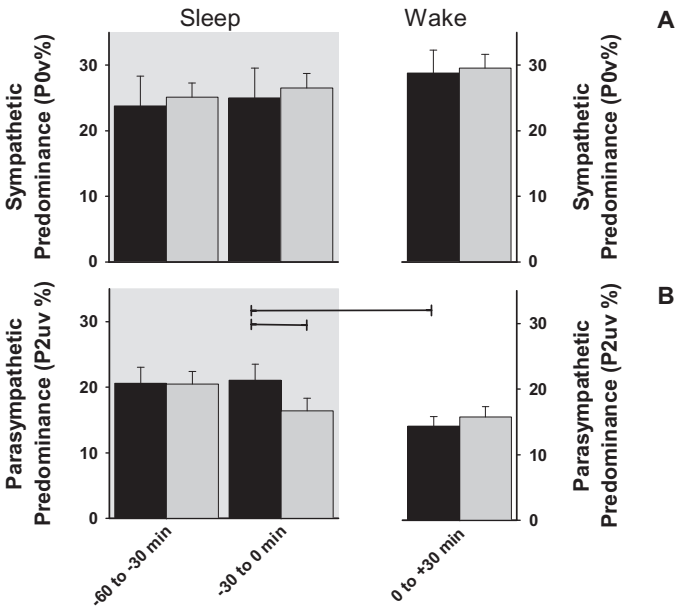

Fig. 2. Symbolic dynamics of HRV. Sympatho-vagal modulation during the transition from sleep to wakefulness under dim light (black) and dawn simulation light (gray). Data were averaged for 30 min bin, separately during sleep without light, gradual light increase and after wake time (0). Error bars represent SEs. Horizontal bar characterize the significant difference between conditions ($p < 0.05$).

Our data are the first demonstration that light exposure surrounding the wake-up process reduces rapid wake-to-sleep evoked increases in heart rate, as well as cardiac sympatho-vagal modulation. This less steep transition enveloping the wake-up process may play a protective role for cardiac events, which usually reach a peak in the early morning hours [1]. Indeed, our data show that dawn simulation light might protect the heart by *an evolving preparation* of cardiac physiology for the wake-up process, which is achieved by a subtle pre-stimulation of cardiac activity during sleep prior awakening. Importantly, these light-induced effects onto cardiac control did not depend on changes in the sleep–wake structure surrounding the wake-up time (see Supplementary Table S1). Thus, the naturalistic light condition *reduces* the temporal abruptness of key cardiac events, which are one of the major reasons for increased cardiac vulnerability in the morning [2].

Salivary cortisol levels were relatively higher following wake-up time, under DSL than the control condition, while no differences were observed in the time-courses after that. One likely explanation is that exposure to DSL condition, which gradually increases from 0 to 250 lux during 30 minutes before wake-up time, may have elicited a phase-advance in the circadian modulation of cortisol levels. Light exposure resets the phase of the internal biological clock, thus impacting on human physiology and behavior [23]. However, acute light effects on cortisol strongly depend on the intensity, duration, and circadian phase of light exposure [24]. As exposure to DSL was in the early hours of the morning that corresponds to the time-window for phase-advancing light effects, it may have phase-advanced the time-course of salivary cortisol. Physiologically, one may translate these results as an earlier "preparation" for wake-up time, which would go in line with our HR and HRV data. However, caution should be made as we did not collect cortisol samples prior to the participant's wake-up time. While our study provides evidence for a significant impact of light as a tool to *gradually prepare* cardiac physiology during the sleep-to-wake time, limitations should be drawn. Our study was designed to probe how light impacts on HR and HRV under normal physiological conditions, as this is a topic that is still fairly unknown.

4. Conclusions

Our current findings provide a proof-of-principle that light may act as an adjuvant in healthy young individuals. Future studies including normal and pathological aging, with the inclusion of biochemical analyses (ie, catecholamine release), may provide a more conclusive framework for the applicability of light as a countermeasure for acute cardiovascular events. Strategies that may counteract these potentially deleterious cardiovascular events are in dire need. In view of our results, light may provide a potentially non-invasive tool to minimize cardiovascular stressful events during the critical morning hours.

Conflict of interest

The authors declare no competing financial interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.12.018.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2014.12.016.

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IV- Morning light effect in young study volunteers

2/ Neurobehavioral performance (cognition)

Dawn simulation light impacts on different cognitive domains under sleep restriction.

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Research report

Dawn simulation light impacts on different cognitive domains under sleep restriction

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HIGHLIGHTS

- We investigated morning light effects on cognition after a night of sleep restriction.
- Morning light effects depend on cognitive domain.
- Morning light effects depend on individual performance levels.

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ABSTRACT

Chronic sleep restriction (SR) has deleterious effects on cognitive performance that can be counteracted by light exposure. However, it is still unknown if naturalistic light settings (dawn simulating light) can enhance daytime cognitive performance in a sustainable matter.

Seventeen participants were enrolled in a 24-h balanced cross-over study, subsequent to SR (6-h of sleep). Two different light settings were administered each morning: a) dawn simulating light (DsL; polychromatic light gradually increasing from 0 to 250 lx during 30 min before wake-up time, with light around 250 lx for 20 min after wake-up time) and b) control dim light (DL; <8 lx). Cognitive tests were performed every 2 h during scheduled wakefulness and questionnaires were completed hourly to assess subjective mood.

The analyses yielded a main effect of "light condition" for the motor tracking task, sustained attention to response task and a working memory task (visual 1 and 3-back task), as well as for the Simple Reaction Time Task, such that participants showed better task performance throughout the day after morning DsL exposure compared to DL. Furthermore, low performers benefited more from the light effects compared to high performers. Conversely, no significant influences from the DsL were found for the Psychomotor Vigilance Task and a contrary effect was observed for the digit symbol substitution test. No light effects were observed for subjective perception of sleepiness, mental effort, concentration and motivation.

Our data indicate that short exposure to artificial morning light may significantly enhance cognitive performance in a domain-specific manner under conditions of mild SR.

1. Introduction

Numerous factors can influence cognitive performance, chief among them are the impact of time of day [1,2] and homeostatic sleep pressure [3]. Chronic sleep restriction (SR) has deleterious effects not only on daytime alertness but also on cognitive performance [4,5].

Indeed, sleep disruption results in specific cognitive impairments including deficits in attention, executive function, non-declarative and declarative memory, as well as emotional reactivity and sensory perception [6–8]. Some studies show that

Abbreviations: NIF, Non-Image Forming; fMRI, functional Magnetic Resonance Imaging; SR, sleep restriction; DsL, Dawn simulation light; DL, dim light; MTT, Motor Tracking Task; DSST, Digit Symbol Substitution Test; PVSAT, Paced Visual Serial Addition Task; simRT, Simple Reaction Time Task; SART, Sustained Attention to Response Task; PVT, Psychomotor Vigilance Task; V1-V2-V3, 1,2,3-back: Visual N-back Task; SC, superior colliculus.

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light exposure can act as countermeasure for these cognitive impairments in humans [9,10].

These acute impacts of light are usually referred to as non-visual (or Non-Image Forming – NIF) effects, since they drift apart from classical involvement of rod and cone photopigments in visual responses to light. NIF light effects at shorter wavelength via novel photoreceptors containing the photopigment melanopsin appear to strongly impact the human circadian timing system [11,12]. Behavioural responses triggered by light encompass improved alertness and performance, as indexed by specific cortical responses to cognitive tasks in Photon Emission Tomography and functional Magnetic Resonance Imaging (fMRI) techniques [13]. However, dosage (intensity and duration), timing and wavelength of light for domestic use and in the workplace environments are difficult to define and may critically depend on environmental and the individual factors.

In a previous study, we have shown that exposure to gradually increasing light prior to awakening can counteract sleep restriction effects on well-being and cognitive performance across the day, leading to an optimized level of alertness, which impinges on enhanced performance on specific cognitive tasks tightly related to sustained levels of attention [14].

Most of the effects were visible on the first day after the sleep restriction night but not on the second day after two nights of sleep restriction, most likely due to the increase in sleep pressure.

The overall aim of the present study was to investigate whether dawn simulation light following sleep restriction, enhances performance according to cognitive domain and whether these effects are sustained during the entire day.

2. Material and methods

2.1. Study participants

Study volunteers were recruited through advertisements at different local universities and websites in Switzerland, Germany and France. Screening procedure began with a telephone interview, involving a detailed study explanation. All participants gave written informed consent before the start of the laboratory part. Study protocol, screening questionnaires and consent forms were approved by the local ethics committee (EKBB/Ethikkommission beider Basel, Switzerland) and conformed to the Declaration of Helsinki.

All applicants completed questionnaires about their sleep quality, life habits and health state. These questionnaires comprised a consent form, a general medical questionnaire, Beck Depression Inventory II [15], Epworth Sleepiness Scale [16], Horne Ostberg Morningness Eveningness Questionnaire [17], Munich Chronotype Questionnaire [18] and Pittsburgh Sleep Quality Index. Potential candidates with a Pittsburgh Sleep Quality Index score >5 were excluded from participation [19]. Further exclusion criteria were smoking, medication or drug consumption, body mass index <19 and >28, shift work and transmeridian flights within the last three months, as well as medical and sleep disorders. Since our study protocol included two nights of partial sleep restriction (restriction to 6-h), we also excluded participants with habitual sleep durations <7-h and >9-h [20], to minimize a possible confounding effects of sleep duration.

Eighteen young men (20–33 years old; mean + Standard Error of Mean: 23.1+.8) fulfilling all the criteria were enrolled in the study. A comprehensive toxicological analysis of urine for drug abuse was carried out before the study, along with an ophthalmologic examination to exclude volunteers with visual impairments.

One week before the study, participants were not allowed to drink excessive alcohol, and to consume caffeine or cacao containing drinks or meals (at most 5 alcoholic beverages per week, and 1 cup of coffee or 1 caffeine-containing beverage per day). They were also instructed to keep a regular sleep-wake schedule (bed and wake times within ±30 min of self-selected target time). Compliance to this outpatient segment of the study was verified by wrist actigraphy (actiwatch L, Cambridge Neurotechnologies, Cambridge, UK) and self-reported sleep logs.

The study was carried out during the winter season (January to March) in Basel, Switzerland, and comprised two segments, distributed in a balanced cross-over design, separated by at least 1-week intervening period. The volunteers reported to the Centre for Chronobiology at the Psychiatric Hospital of the University of Basel on two occasions (control condition and one experimental conditions), where they stayed in individual windowless bedrooms with no information about time of day. Since we did not find significant effects on cognitive performance neither after the blue light exposure nor after the DsL exposure after the second night of sleep restriction, we decided to focus here on the first 24-h of the control condition and the DsL condition. The most likely explanation was that sleep pressure was too high after the second night of sleep restriction, and thus the morning light could not counteract its

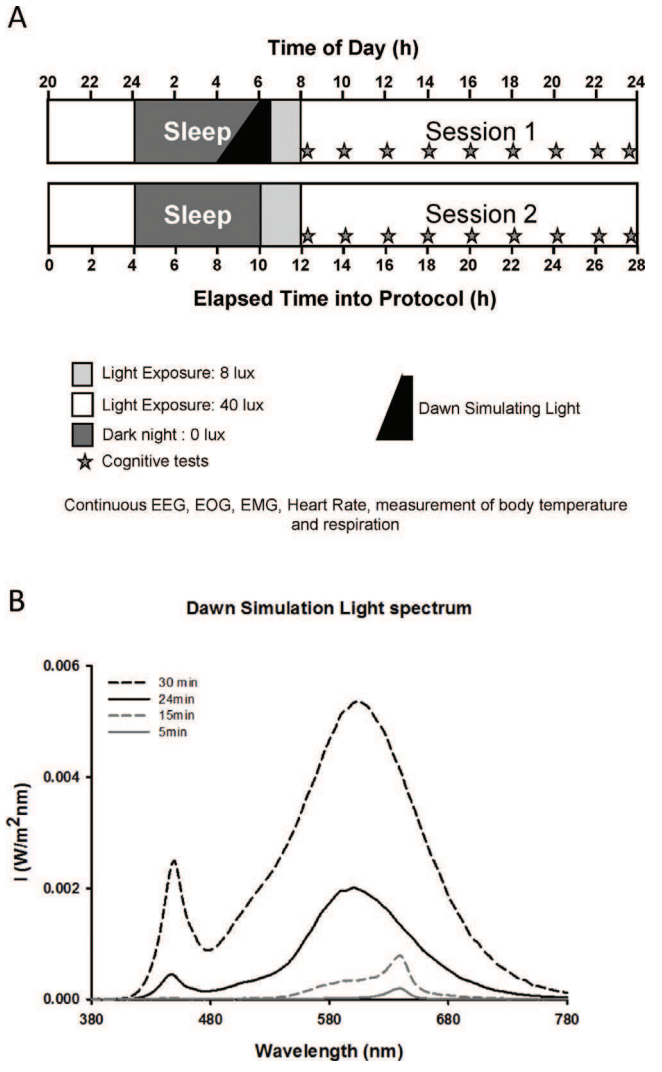

Fig. 1. (A) **Protocol design**. Two arms of a 6-h sleep restricted protocol with different morning light exposures. Elapsed time indication is relative to an arrival in the lab at 8 p.m. Time-of-day indication varied across all subjects but was given in the figure as an example (taken from the mean of the sleep/wake time from all participants). (B) **Morning light device.** Spectral composition (light wavelength by irradiance (W/m2nm)) of the Dawn Simulation Light at 5 min (grey solid), 15 min (grey dash), 24 min (black solid) and 30 min (black dash).

detrimental effect. For more details, referred to Gabel et al. [14]. These 24-h include the first sleep restriction night (6-h) at 0 lx starting at the subject's habitual sleep time and followed by 18-h of data recording during wakefulness. During the day, in both conditions, participants were exposed to dim light (<8 lx) during 2-h after wake-up and to 40 lx for the remainder of the day until they went to bed (Fig. 1A). In both conditions, the investigator enters the room in the morning, 6-h after light off, to wake-up the participants.

The light treatment was administered after the sleep restriction night either with no additional light for the control condition or with a Dawn Simulation Light (DsL: LED prototype of Philips Wake-up Light HF3520, Philips Drachten, The Netherlands) (polychromatic light gradually increasing from 0 to 250 lx during 30 min before wake-up time; the light remains around 250 lx for 20 min after wake-up time), placed near the bed at eyes level (Fig. 1B). One participant could not be included in the analysis because of poor quality of the electroencephalogram recordings and non-compliance during cognitive testing. The remaining 17 volunteers underwent both light conditions in a balanced cross-over design as follows: DL–DsL for nine volunteers and DsL–DL for eight.

2.2. Assessment of subjective ratings

Subjective sleepiness was assessed every hour with a Visual Analogue Scale (100 mm scale). Likewise, after every test session participant had to indicate the effort, concentration and motivation they needed to perform the tests. A 100 mm effort visual analogue scale was used, ranging from "0:little" to "100:much" [21,22].

2.3. Cognitive performance

All tests were administered every 2 h during wakefulness, starting 30 min after wake up. The test battery comprised the Motor Tracking Task (MTT), Digit Symbol Substitution Test (DSST) [23], Paced Visual Serial Addition Task (PVSAT) [24,25], Sustained Attention to Response Task (SART) [26], Psychomotor Vigilance Task (PVT) [27], Simple Reaction Time Task (simRT) and Visual N-back Task (1,2,3-back) [28]. For detailed information about each test, please see Table 1.

All the results are given relative to elapsed time after wake-up from restricted sleep taken at 6 a.m. Time-of-day indication was also added to be more informative and understandable for general public; it is an example calculated with the mean of the participants sleep/wake cycle, as they did not have the same scheduled time.

2.4. Statistical analysis

For all analyses, the statistical package SAS (version 9.1; SAS Institute, Cary, NC, USA) was used. Statistical analyses were carried out for each variable (subjective fatigue, motivation, concentration, effort, PVT, MTT, DSST, SimRT, SART, PVSAT and N-Back) separately with the mixed-model analysis of variance for repeated measures

Table 1
Description of the tasks in the cognitive test battery.

Tests	Cognitive domain	Explanation of the tests	References
Motor Tracking Task (MTT)		People need to track a computer-generated disc using the mouse, along another computer-generated point for 20 s	
Digit Symbol Substitution Test (DSST)	Computer-based "cognitive throughput" task (or attention-based task) measuring clerical speed and accuracy. The task becomes less sensitive to changes in attention and more sensitive to memory impairment.	Participants are required to select a predefined digit in response to each appearance of an abstract symbol (the key linking symbols and digits are available on screen throughout testing). They learn the coding relationships after some experience. In this paced version of the task, 8 symbols are presented for 500 ms, with an ISI of 1500 ms. Each symbol occur an equal number of times.	Aster et al. [23]
Paced Visual Serial Addition Task (PVSAT)	Addition task heavily dependent on frontal brain regions, involving executive aspects of working memory	Single digits (1 to 9) appear on screen and each must be added to the digit which preceded it, and the resulting answer is selected from an on-screen numerical keypad ("sum" of adjacent pairs, not a total across all digits presented). Digits were seen for 1000 ms, with inter-stimulus interval (ISI) of 2000 ms in between.	Feinstein et al. [24]; Nagels et al. [25]
Sustained Attention to Response Task (SART)	Sustained/divided attention task in which inattention and inhibitory processing can be measured separately. Both types of performance depend on the frontal cortex	It's a computer-based task, used here as a Go/NoGo task, which requires participants to monitor single digits presented rapidly on screen, and respond to each one that appears (called Go target), except for a particular pre-defined digit (called NoGo target). Digits are presented for 1000 ms, with an inter-item interval of 2000 ms, with 15 "targets" (where responses are withheld) randomly interspersed with 25 distractors.	Robertson et al. [26]
Psychomotor vigilance task (PVT)	Sustained attention task, sensitive to circadian variation and sleep loss It is an approach of Dinges (Dinges, Pack et al., 1997).	The PVT involves a 5-min visual reaction time (RT) performance test in which the subject is required to maintain the fastest possible RT's to a simple auditory stimulus. Data analyses focus on RT, errors, and signal detection theory parameters.	Dinges et al. [27]
Simple Reaction Time Task (simRT)	Indicator of speeded motor performance. Vary as a function of alertness and sleep deprivation	This task requires people to respond, as quickly as possible, to a single, predictable stimulus. The participant rests his/her index finger on a mouse, and having done so over the next 1000 ms a word such as "Now!" appears, at which point the participant moves the cursor to a designated target position. The time taken from Now! To the onset to move the cursor from the resting position reflects the participants' ability to detect that a response is required, and, together with the subsequent time taken to move the mouse to the target position, give us the RT.	
Visual N-back Task (1,2,3-back)	Executive aspects of working memory	Stimuli are presented individually on a computer screen, and the participant must indicate (using the mouse), if the current stimulus and the n stimuli prior to it match. The higher the n, the stronger are the demands of executive functioning. Stimuli are presented for 500 ms with an ISI of 1500 ms. The ratio between match to non-match trials is of 1: 2 with 30 items.	Cohen et al. [28]

Table 2
Results of the analysis of the variance for different variables of subjective feeling for the time course of the study.

Variable	Analysis of the variance		
	Light	Time of day	Light × Time
Effort	$F_{1,254} = 0.14$, $p = .7059$	$F_{8,254} = 1.21$, $p = .2927$	$F_{8,254} = 51$, $p = .8485$
Concentration	$F_{1,254} = .69$, $p = .4061$	$F_{8,254} = 1.42$, $p = .1877$	$F_{8,254} = 1.08$, $p = .3806$
Motivation	$F_{1,254} = 2.87$, $p = .0913$	$F_{8,254} = 1.56$, $p = .1377$	$F_{8,254} = .45$, $p = .8927$
Fatigue	$F_{1,254} = 00$, $p = .9996$	$F_{8,254} = 4.28$, $p < .0001$	$F_{8,254} = 1.07$, $p = .3830$

(PROC MIXED), with within factors "light condition" (dim light [DL] versus dawn simulation light [DsL]) and "time-of-day" (all assessed time points).

A further analysis included the factor "group" was done, according to the subject's performance on the 3-back task. As this working memory paradigm presents a relatively high cognitive load it might be suitable to differ between high and low performers. Thus, we performed a median split and considered subjects presenting performances below the median of the overall group as low performers ($N = 9$) and those above as high performers ($N = 8$).

3. Results

3.1. Assessment of subjective ratings

No significant differences were found between light conditions for effort, concentration and motivation needed to perform the tasks. Similarly, subjective sleepiness induced by the test did not differ across the light conditions (Table 2). For detailed information on sleepiness, well-being and mood, please see [14].

3.2. Cognitive performance

3.2.1. MTT

Main effects of "light condition" and "time-of-day" were observed for the MTT (Table 3), such that after the DsL exposure participants were better at following the dot than after the DL exposure during the entire day (Fig 2B).

3.2.2. DSST

Main effects of "light condition" and "time-of-day" were also observed for DSST (Table 3) but in the opposite direction. Participants performed better after the DL exposure than after the DsL exposure throughout the day (Fig. 2A).

3.2.3. PVSAT

PVSAT performance did not yield significant differences neither for the main factors "light condition", nor for the interaction of "light condition × time of day" (Table 3). Only the factor "time of day" was significant such that participants improved their performance across the day independent of light treatment (data not shown in the figure).

3.2.4. SART

Main effect of "light condition" (Table 3) was observed for accuracy (correct answers for Go and NoGo targets), such that until 5-h of time awake, the performance was not significantly different irrespective of light settings, while 6-h after wake-time DsL improved performance along the day as compared to DL (Fig. 2D).

Besides, NoGo trials were analyzed as a proxy for inhibition control. It revealed a main effect of "light condition" ($p = 0.0013$). Participants had less correct NoGo answers after the DsL exposure than after the DL exposure and mostly at the beginning of the day. Furthermore, the missed answers (missed Go answers) showed a main effect of "light condition" ($p < 0.0001$), such that the DsL led to lower levels of missed answers than the DL. The reaction time for this task showed also a significant trend of the "light condition" effect ($p = 0.0876$), such that participants answered faster at the beginning of the day after the DsL.

3.2.5. PVT/simRT

The DsL exposure did not influence reaction time during the PVT (Table 3, data not shown in the figure) and performance was similar after both light exposures. However, the DsL decreased reaction time in the SimRT test throughout the day, as shown by a main effect of "light condition" and "time of day" (Table 3, Fig. 2C).

3.2.6. N-BACK

The 1-Back showed a main effect of "light condition" (Table 3) for accuracy, driven by DsL exposure. After 4-h of elapsed time awake, DsL improved accuracy, with a stronger effect in the evening, while performance remained stable after DL exposure (Fig. 2E).

No significant differences were found between both light conditions in the 2-Back test (data not shown in the figure).

For the 3-Back test, we found a main effect of "light condition", such that participants had a higher rate of correct answers after a DsL than after a DL exposure, starting at the beginning of the day and remaining all the day (Fig. 2F).

Table 3
Results of the analysis of the variance for different variables of cognitive performance for the time course of the study.

Variable	Analysis of variance		
	Light	Time of day	Light × Time
MTT	$F_{1,260} = 1.76$, $p = .0079$	$F_{8,260} = 2.05$, $p = .0407$	$F_{8,260} = .58$, $p = .7933$
DSST	$F_{1,254} = 7.22$, $p = .0077$	$F_{8,254} = 2.44$, $p = .0148$	$F_{8,254} = .25$, $p = .9800$
SimRT	$F_{1,271} = 5.52$, $p = .0195$	$F_{8,271} = 3.07$, $p = .0025$	$F_{8,271} = .33$, $p = .9554$
PVT	$F_{1,264} = 3.31$, $p = .0700$	$F_{8,264} = 1.95$, $p = .0528$	$F_{8,264} = .44$, $p = .8933$
SART	$F_{1,255} = 5.07$, $p = .0252$	$F_{8,255} = .28$, $p = .9731$	$F_{8,255} = .31$, $p = .9601$
PVSAT	$F_{1,272} = 0.96$, $p = .3277$	$F_{8,272} = 2.42$, $p = .0152$	$F_{8,272} = .90$, $p = .5204$
1-Back	$F_{1,255} = 5.86$, $p = .0162$	$F_{8,255} = .66$, $p = .7269$	$F_{8,255} = .88$, $p = .5368$
2-Back	$F_{1,255} = 0.04$, $p = .8323$	$F_{8,255} = .56$, $p = .8127$	$F_{8,255} = 1.12$, $p = .3497$
3-Back	$F_{1,254} = 16.69$, $p < .0001$	$F_{8,254} = .48$, $p = .8716$	$F_{8,254} = .16$, $p = .9952$

MTT: Motor Tracking Task; DSST: Digit Symbol Substitution Test; SimRT: Simple Reaction Time Task; PVT: Psychomotor Vigilance Task; SART: Sustained Attention to Response Task; PVSAT: Paced Visual Serial Addition Task; 1-2-3-Back: Visual N-back Task.

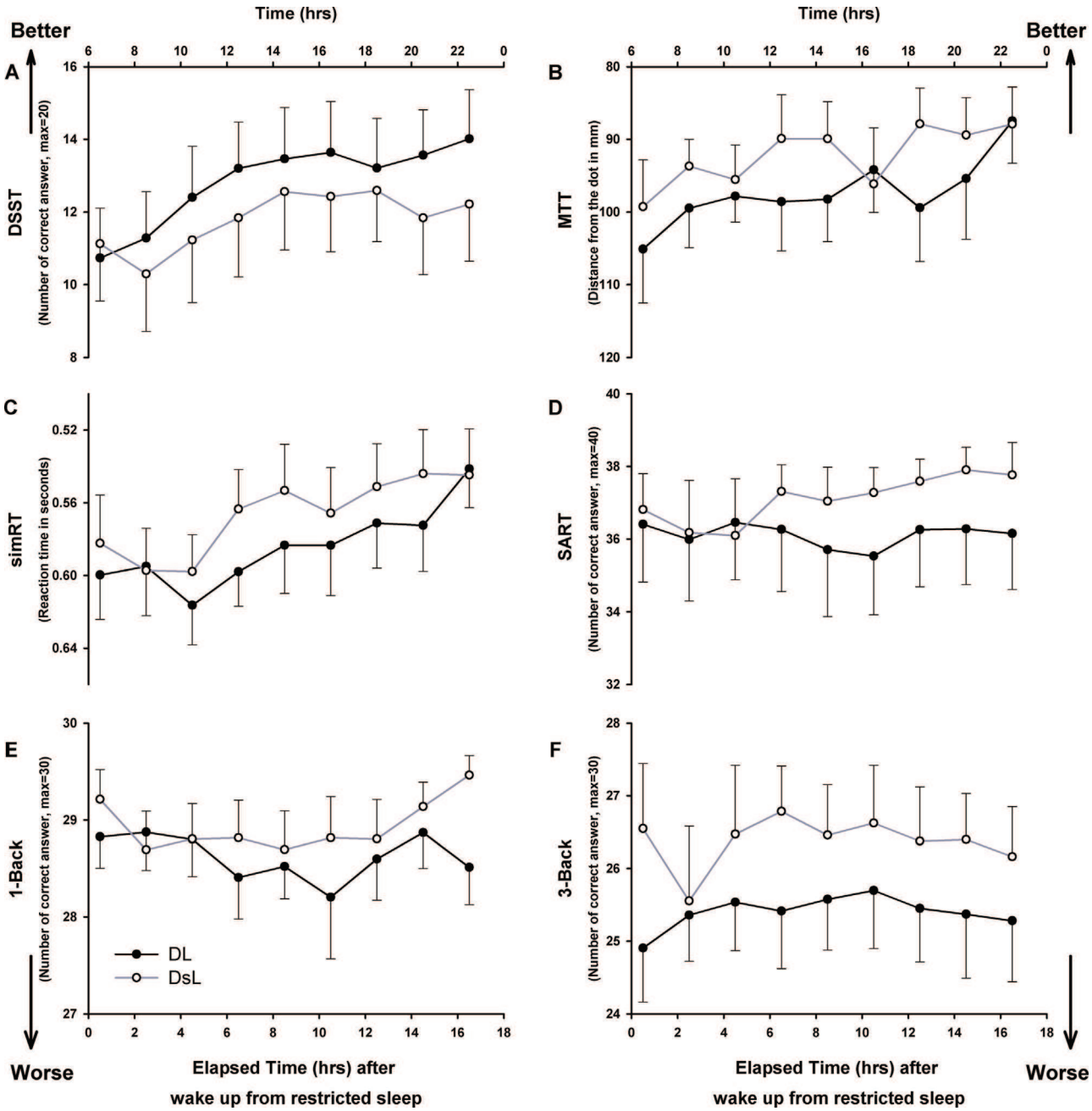

Fig. 2. Accuracy of the cognitive performance over the day.
Time course of the (A) Digit Symbol Substitution Test (DSST), the (B) Motor Tracking Task (MTT), the (C) Simple Reaction Time Task (simRT), the (D) Sustained Attention to Response Task (SART), the (E) Visual 1-back Task (1-Back) and the (F) Visual 3-back Task (3-Back) in 17 participants under Dim light (black lines) or Dawn Simulation Light (grey lines with black circle). Data are plotted as a mean for each 2-h bin relative to elapsed time (h) after wake-up from restricted sleep, and the error bars represent the standard error of the mean. Elapsed time indication is relative to 6 a.m. wake-up time.

3.2.7. *Reaction times*

Furthermore, the composite score of the reaction time from those cognitive tests presenting higher cognitive load (n-Back, SART, PVSAT) was significantly lower after the DsL than after the DL (supplementary data).

3.3. *High vs. low performers*

Splitting the group according to high and low performance, a main effect of "light condition" was present in the low but not in the high performers, such that the DsL light improved performance in the PVSAT ($p = 0.0096$), the 3-Back test ($p < 0.0001$) and the simRT test ($p = 0.0064$) compared to the DL condition (Fig. 3).

4. Discussion

Our data show that artificial morning light exposure, as indexed by DsL, has a task-dependent effect on cognitive performance under sleep restriction conditions, such that morning DsL significantly enhanced performance on attention-based tasks (SART, 1-verbal Back, and simRT). Furthermore, DsL significantly improved performance on the MTT that involves motor-based skills, and the 3-verbal back, which mostly probes executive function. However,

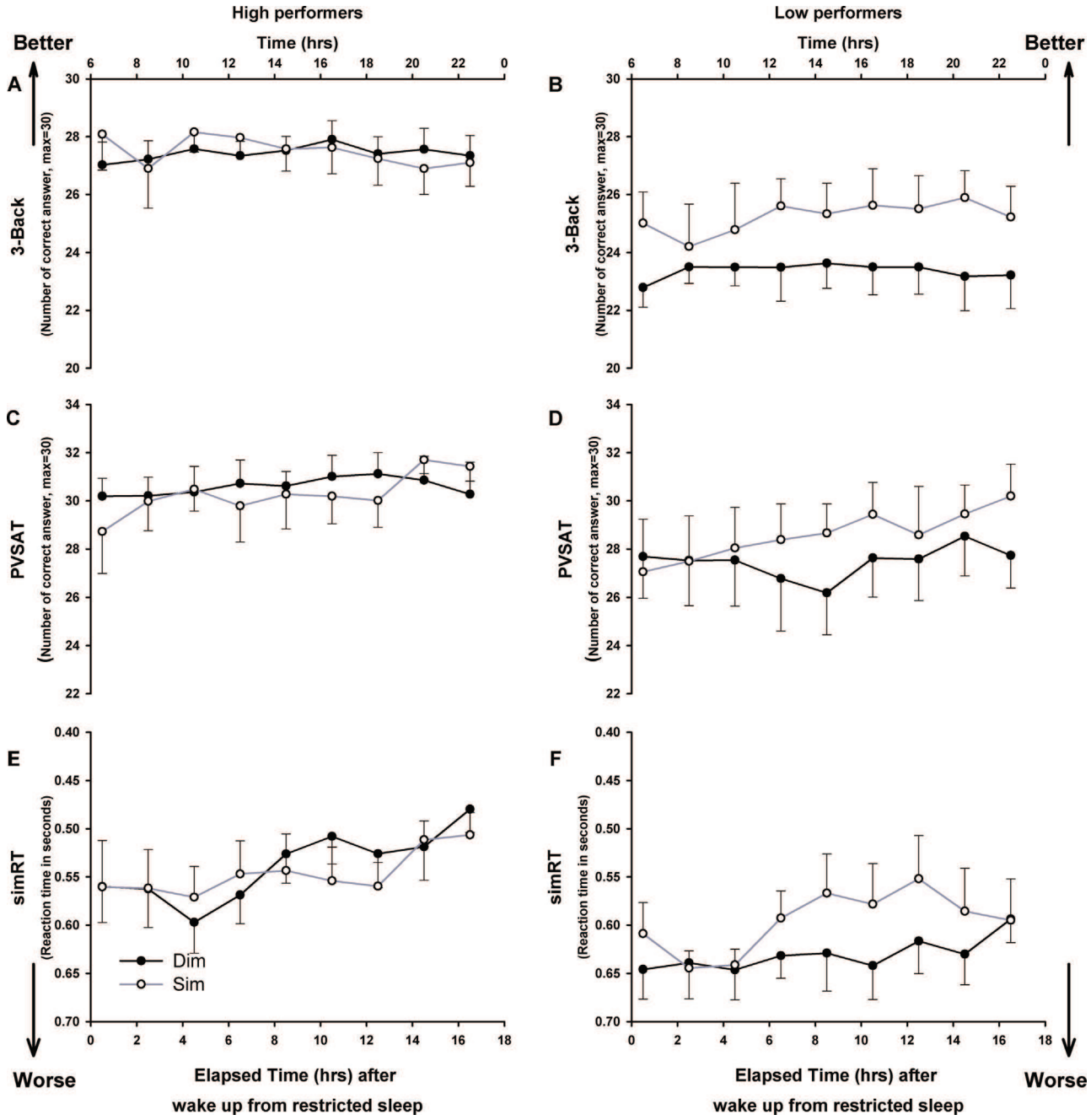

Fig. 3. Accuracy of the cognitive performance over the day in the high and low performers.
Time course of the high performers (left panel) and the low performers (right panel) of the (A) Visual 3-Back (3-Back), the (B) the Paced Visual Serial Addition Task (PVSAT) and the (3) Simple Reaction Time Task (simRT) in 17 participants under Dim light (black lines) or Dawn Simulation Light (grey lines with black circle). Data are plotted as a mean for each 2-h bin relative to elapsed time (h) after wake-up from restricted sleep, and the error bars represent the standard error of the mean. Elapsed time indication is relative to 6 a.m. wake-up time.

we also found better performance after the DL compared to the DsL for the DSST.

Our results corroborate our previous analysis that artificial morning dawn simulation light improves subjective perception of well-being and mood, as well as cognitive performance across the day under conditions of mild sleep restriction [14]. However, here we showed that the light effect on performance depends on the investigated cognitive domain, suggesting that different pathways may be implicated in this effect. Previous studies indicate that evening light exposure impacts on numerous domains of cognitive performance such as sustained attention [10], working memory and attention, as well as declarative memory [9].

Here we show that light exposure during the morning hours can significantly boost cognitive performance and maintain its stability throughout the day. Most studies on the effects of light in humans have been carried out during the night, when light is able to counteract the increasing sleep pressure, and thus significantly enhance or stabilize cognitive performance (for a review, see [29]). In this context, the modulatory mechanisms accounting for the light effects on cognition have been ascribed to its impact on sleep homeostasis and/or its indirect synchronizing/phase-shifting effects on the circadian timing system [10]. However, alternative mechanisms may bypass these systems, thus eliciting direct activating effects, particularly when light is timed during the day.

Evidence for the latter arises from studies in which daytime performance increased after 30 min from light onset [30,31], from an fMRI study in which daytime light enhanced cognitive brain activity during an oddball task [32] and from our previous analysis in which morning light exposure (dawn simulation light) increased well-being and enhanced performances across the day [14]. Recently, another study showed the critical role of light for cognitive brain responses in emphasizing the evidence of a cognitive role for melanopsin, which may confer a form of "photic memory" to human cognitive brain function [33]. Collectively, these data suggest that light may modulate ongoing cortical activity involved in alertness, thus stimulating cognitive brain function.

One crucial brain region involved in the impact of light on cognition is the anterior hypothalamus, in locations compatible with the suprachiasmatic nucleus and the ventrolateral preoptic nucleus [34]. This region is postulated to be the primary link of the retina to the brain, thus mediating the effect of light on cognition [13]. Furthermore, numerous retinal projections extend to the lateral geniculate nucleus and also (albeit less) to the superior colliculus (SC). From the lateral geniculate nucleus, projections are sent to the primary visual cortex, which is the first processing site of the cortical visual pathway. Functionally, this pathway is classified in dorsal and ventral streams [35]. The former is associated to motion processing (medial temporal and superior temporal, and also parietal cortices), while the latter involves salient visual processing [36]. Interestingly, attention-related modulatory effects impact on both streams. Within the dorsal stream, attention is "encoded" by neurons involved in spatial attention/feature-based attention, such as the orientation of an object or a moving dot [36]. Concomitantly, motion-sensitive medial temporal and superior temporal areas are also involved in these processes, as well as higher cortical areas such as the intraparietal cortex [37]. We tentatively speculate that this particular network may be underlying the responses in the MTT task, and that light might play a modulatory role on this type of spatial attention/feature-based attention.

With respect to the ventral attention-based stream, a key structure involved in this attentional network is the SC, which receives direct input from the retina. This attention network is presumably shared with the intraparietal region [38], frontal eye fields [39], and visual cortices, through direct connections from the cortex to the SC, and indirectly from the SC to the cortex via the pulvinar [40]. The pulvinar (dorsal thalamic nuclei) is pivotal in attention modulation, presumably through the flow of information in the brain. It receives a direct retinal projection, and provides an indirect link between the suprachiasmatic nucleus and the prefrontal cortex [41]. Thus, it mediates arousal regulation, and an effect of light on the thalamus will probably result in a widespread cortical impact, such as on attention-based cognitive performance. Taken together, we postulate that these brain networks may underlie the modulatory light effects on numerous dimensions of attention tasks, such as on MTT, 1-Back, simRT and SART. It could also explain the lack of correct NoGo answers and the decrease of the missed Go answers in the SART test after the DsL exposure. Effectively, arousal levels are more prominent at the beginning of the day and might even be more pronounced after a light exposure, which explains response accuracy at the beginning of the day. However, different tasks require different levels of arousal for optimal performance [42]. For example, difficult or intellectually demanding tasks may require a lower level of arousal (to facilitate concentration), whereas tasks demanding stamina or persistence may be performed better with higher levels of arousal (to increase motivation) [43]. According to this concept, it could be argued that the arousal level after the DsL exposure was too high to inhibit the participant's answers in the SART task, which is in accordance with the increase of the reaction time in this task during the first hours after wake time. This leads to a speed-accuracy trade-off in the inhibitory process, meaning that light exposure induces higher excitability resulting in faster reaction time and thus in lack of inhibition control.

Our PVT data did not parallel earlier findings of a beneficial light effect [10,30]. One possibility is that, contrary to our design, these studies challenged sustained attention performance either during light exposure and did not specifically explore carry-over effects or after a prolonged daytime light exposure. However they are comparable to the findings from Van de Werken [44], showing that the reaction times under DsL were similar to the one under control condition. One could argue that the PVT needs a higher and, more probably, a sustained level of arousal than the SART test – which is not reached here – to get to optimal performance levels, since this task is much more monotonous with much fewer stimuli (e.g., [45]). The absence of a significant effect could be traced back to the fact that we compared reaction times after one night of sleep restriction between two light conditions. This is different to other studies, comparing rested wakefulness to sleep deprived or sleep restricted conditions. Similarly, the DSST showed the contrary of the expected effect, such that participants were slower in reacting and less accurate. We have no straightforward explanation for the opposing effect of the DSST. It cannot be due to a simple learning effect across conditions as we counterbalanced the order and we did not detect a significant interaction between time of day and condition. Neither the observed pattern can be attributed to general impairments in working memory functions across the day under DsL as we found better performance under DsL for the n-Back test. These two tasks were the first two tasks administered within each testing sessions, thus, a certain time-on-task effect can be ruled out, and a floor effect of light impact because of high demand is equally implausible.

Interestingly, our data also show a significant DsL effect on the 3-verbal back task. This task challenges working memory, which refers to the individual capacity to temporarily maintain active relevant information to perform an ongoing task [46,47]. This task involves the need to continuously update and inhibit information, and also has an attentional component to it. Thus, one possible explanation to the DsL effects is that light may enhance performance on the 3-back task via its impact on the basic attention component in this complex working-memory task. However, at the behavioural level, it is not possible to dissect out the components existing within this task. Thus, light might also impact on the executive component of this task. The 3-back task probes executive control, and its cerebral correlates involve the bilateral posterior parietal cortex, premotor cortex, dorsal cingulate/medial premotor cortex, dorsolateral prefrontal cortex and ventrolateral prefrontal cortex [48]. Light may have a modulatory effect on these anatomical structures, thus impacting on executive brain responses [49].

Furthermore, light has greater beneficial effects on the low performers (stratified according to the 3-Back results) compared to the high performers in the 3-back, PVSAT and simRT. However, it is important to consider a potential ceiling effect for the high performers; as the sleep restriction was not that severe, these participants could easily cope with this and thus, keep their high level of performance. Thereby, the impact of light might have been difficult to detect.

Interestingly, the low performers on the 3-back who profit most from the light intervention are also the ones who experience a detrimental effect of light on their reaction times in the PVT. This is somewhat contra-intuitive, as we previously showed that light leads to faster reaction time [10]. However, it could indicate that the low performers are more cautious in their task performance under the effect of light, and therefore profit in a complex task, where accuracy is important, but decline in a more basic task where fast reactions are required. Clearly, it indicates that the light effect is dependent on the cognitive domain and obviously also acts differentially depending on how well someone performs.

5. Conclusion

Our results collectively indicate that short exposure to gradually increasing morning light (DsL) just before the end of the partially restricted night episode, may significantly enhance performance, particularly in cognitive tasks associated to attention. In a broader context, these findings point to strategies that may directly optimize attention-related cognition in real-life settings, particularly when individuals are sleep restricted.

Supplementary data

Reaction time from the cognitive tests over the day. Time course of the composite of reaction time of the Paced Visual Serial Addition Task (PVSAT), Sustained Attention to Response Task (SART) and Visual 1-2-3-back Task (1-2-3-Back) in 17 participants under Dim light (black lines) or Dawn Simulation Light (grey lines with black circle). Data are plotted as a mean for each 2-h bin relative to elapsed time (h) after wake-up from restricted sleep, and the error bars represent the standard error of the mean. Elapsed time indication is relative to 6 a.m. wake-up time.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2014.12.043.

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V- Extended light exposure

1/ Age dependent effects on circadian physiology and alertness

Differential impact of blue-enriched white light on circadian physiology and alertness during sustained wakefulness in young and older individuals.

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Under correction.

Differential impact of blue-enriched white light on circadian physiology and alertness during sustained wakefulness in young and older individuals

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Running title: Age-related light effect on circadian physiology and alertness

Key words: Aging, Light, sleep deprivation

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KEY POINTS

- Light has acute non-visual effects on human physiology and behaviour, particularly when administered in the late evening
- Aging alters the circadian rhythm and the response to light
- We investigated whether an extended white and blue-enriched white light exposure has the same effect in young and older volunteers on sleepiness and circadian profiles of melatonin, cortisol, skin temperature and motor activity levels after 40-h of extended wakefulness
- Both light decreased subjective sleepiness in both age groups. Melatonin was only suppressed in the young, and even more under blue-enriched light. Only the blue-enriched light modified cortisol level, with a decrease in the young and an increased in the older. Both light had a contrary effect depending on the age of the participant in regard to skin temperature and motor activity
- This work provides evidence that light devices and intensity should be adapted depending on the targeted population

ABSTRACT

We examined the role of extended light exposure as a countermeasure for sleep-loss related decrements in sleepiness and on circadian profiles of melatonin, cortisol, skin temperature and motor activity levels in young and older volunteers.

Twenty-six young [mean (SE): 25.0 (0.6) y)] and twelve older participants [(mean (SE): 63.6 (1.3) y)] underwent 40-h of extended wakefulness once under dim light (DL: 8 lux), and once under either white light (WL: 250 lux) or blue-enriched white light (BL: 250 lux) exposure. Subjective sleepiness was assessed hourly as well as melatonin and cortisol assays. Skin temperatures and motor activity were continuously recorded.

Moderately bright light (WL and BL) during sustained wakefulness induced a significant alerting response in both the older and the young participants. In contrast, we found melatonin suppression only in the young participants with a stronger effect under blue-enriched white light. Cortisol levels were significantly increased in the older compared to the young only under BL. Furthermore, both proximal and distal skin temperatures showed an age-related decrease, which was counteracted by blue-enriched light in the older, particularly in distal skin regions. Older participants moved less compared to the young, but only the young became more active under blue-enriched light.

There is an age-related modulation of the non-visual response to light at 250 lux under extended wakefulness. Thus, the use of moderately bright light in night work and shift work settings, where constant light levels are very common, may have differential effects on circadian physiology in young and older workers.

ABBREVIATION

BDI-II, Beck Depression Inventory II; BL, Blue-enriched white Light; BMI, body mass index; CBT, core body temperature; DL, Dim Light; Mel-off, melatonin offset; Mel-on, melatonin onset; DPG, distal-to-proximal skin temperature gradient; DT, distal skin temperature; ESS, Epworth Sleepiness Scale; ipRGC, intrinsic photosensitive retinal ganglion cells; KSS, Karolinska Sleepiness Scale; MCTQ, Munich Chronotype Questionnaire; MEQ, Horne Ostberg Morningness Eveningness Questionnaire; PRC, phase response curve; PSQI, Pittsburgh Sleep Quality Index; PT, proximal skin temperature; SCN, suprachiasmatic nucleus; SD, sleep deprivation; WL, White Light

INTRODUCTION

Human sleep and physiology as well as alertness and cognitive performance are regulated by a fine-tuned interaction of circadian and homeostatic processes that provide optimal cognition and alertness levels during a 16-h episode of wakefulness, and consolidated sleep during an 8-h nocturnal sleep episode (Cajochen *et al.*, 2010). It is of crucial importance to "see" the light, particularly in the morning and evening in order to entrain human circadian rhythms to the 24-h earth rotation (Czeisler & Gooley, 2007). So far, it is unclear whether sleep homeostatic processes are also affected by light *per se*. However, besides the role of light to act as a "zeitgeber" (i.e. synchronizer) for entraining endogenous circadian rhythms to external 24-h rhythms in the environment, there is ample new evidence that light has also acute non-visual effects on human physiology, cognitive performance, alertness and well-being (Van De Werken *et al.*, 2010; Chellappa *et al.*, 2011a; Gabel *et al.*, 2013). Light suppresses the hormone melatonin and subjective sleepiness as well as its electrophysiological correlates, particularly when administered in the late evening (Cajochen *et al.*, 2000; Lockley *et al.*, 2006; Chellappa *et al.*, 2011b). Studies investigating the impact of daytime light on circadian physiology and alertness levels are less abundant (Phipps-Nelson *et al.*, 2003; Ruger *et al.*, 2005; Vandewalle *et al.*, 2006; Smolders *et al.*, 2012), and whether extended light exposure has a sustained alerting, melatonin suppressing and cognitive performance-enhancing effect during extended wakefulness in young and older volunteers has not been investigated so far.

With healthy ageing, distinct alterations in sleep and cognition as well as light perception occur. Sleep becomes usually more fragmented, and the proportion of deep sleep (slow wave sleep) and sleep spindles are decreasing concomitant with a decrease in psychomotor vigilance performance (i.e., increase in reaction time) and impaired learning capacities with age (Cajochen *et al.*, 2006; Schmidt *et al.*, 2012). The above mentioned circadian disturbances observed in the older population could have originated at different systemic levels: at the input level (i.e., the eyes), the pacemaker level (i.e., suprachiasmatic nuclei in the hypothalamus) or at the output level (i.e., specific structures, which are influenced by the circadian pacemaker). Since light perception changes with ageing, it is very likely that the input level (i.e., the eyes) plays a major role in possible circadian alteration with ageing. Human

visual functions decline with age. There are a number of age-related changes in the eye that may contribute to reduced levels of light reaching the retina, such as the reduction in pupil size (Weale, 1985; Daneault *et al.*, 2012), changes in spectral transmittance of the eyes crystalline lens and in ocular media density attenuate short-wavelength light, modifying the spectral balance of broadband lights at the retina(Coren & Girgus, 1972; Charman, 2003). Altogether, these changes could reduce the amount of light input to the circadian clock - the suprachiasmatic nuclei, whose endogenous oscillations are entrained by environmental light (Ralph *et al.*, 1990). Thus, with age there would be a decreased response to light, which may potentially lead to desynchronization of circadian rhythms (Duffy *et al.*, 2007). Yellowing of the human lens is a well-known age-related change of the ocular media (Xu *et al.*, 1997). It decreases the transmittance of visible light especially in the short wavelength range (van den Berg & Tan, 1994). Some of these age related alterations could also be responsible for the earlier waking times and earlier circadian phases for core body temperature and melatonin rhythms observed in many elderly when compared with young adults (Duffy *et al.*, 1998).

Furthermore, little is known on whether improving light perception (i.e., enhancing the zeitgeber stimulus) in older people may help to improve physiological degradations associated with age. Some researchers showed an increased level of melatonin in older people after increasing environmental light intensity (Mishima *et al.*, 2001) and even no changes in endogenous circadian amplitude of the plasma melatonin rhythm in healthy older people compared to young people (Zeitzer *et al.*, 1999). These findings contradict the postulate that the decrease in melatonin concentration is an age-related characteristic. Therefore, an investigation of the beneficial effects of light, in particular the role of blue-enriched light on sleepiness and circadian regulation of physiological variables in older people is of crucial importance: first because of our ageing society, and second, because of the growing use of blue-enriched light sources due to new lighting technologies (e.g. LED).

In this study, we aimed at investigating the physiological and behavioural consequences of different light exposure regimes on alertness and circadian melatonin, cortisol, activity and core body temperature rhythms in young and older volunteers during 40 hours of sustained wakefulness. Based on the findings

summarized above, we hypothesised that extended blue-enriched white light exposure will alert young more than older participants. We predicted that physiological responses will be affected by light in comparison to dim light exposure. However, these modifications will be different with respect to age and light exposure condition. Our hypothesis was a more pronounced suppression response under blue-enriched than under non-blue enriched white light in both group but less so in the older.

MATERIEL AND METHODS

Ethical Approval

All participants gave written informed consent. The study protocol, screening questionnaires and consent forms were approved by the local ethics committee (EKBB/Ethikkommission beider Basel, Switzerland), and all conformed to the Declaration of Helsinki.

Study participants

Study volunteers were recruited through advertisements at different local universities and internet sites in Switzerland, Germany and France. The screening procedure began with a telephone interview, involving a detailed explanation of the study. All participants completed a consent form, a General Medical Questionnaire, the Beck Depression Inventory II (BDI-II) (Beck *et al.*, 1961), the Epworth Sleepiness Scale (ESS) (Johns, 1991), the Horne Ostberg Morningness Eveningness Questionnaire (MEQ) (Horne & Ostberg, 1976), the Munich Chronotype Questionnaire (MCTQ) (Roenneberg *et al.*, 2003) and the Pittsburgh Sleep Quality Index (PSQI). We excluded participants with general medical, current or past psychiatric and sleep disorders and usual sleep duration of less than seven or more than nine hours. PSQI values were requested to lie below five and BDI-II values below 12. Further exclusion criteria encompassed smoking, medication (except oral contraceptives), or drug consumption. To control for circadian phase misalignment, we excluded shift workers, and study applicants who had trans-meridian flights during three months before study participation. All women were tested for pregnancy prior to the start of

the study. Women without hormonal contraceptive use were tested during the luteal phase of their menstrual cycle.

One week before the study, the volunteers were requested to abstain from excessive alcohol and caffeine consumption to prevent withdrawal effects. Furthermore, they were instructed to keep a regular sleep-wake schedule (8-h sleep at night and no daytime naps) to ensure stable circadian entrainment. Compliance to this outpatient segment of the study was verified using wrist actigraphs (actiwatch L, Cambridge Neurotechnologies, Cambridge, UK) and self-reported sleep logs.

To rule out sleep disturbances and to assess their ability to sleep in a new environment, participants slept one night at the Centre for Chronobiology prior study begin. They also underwent a medical screening to guarantee physical and mental health, as well as an ophthalmologic examination in order to exclude volunteers with visual impairments (visual field, colour vision, pupillary reflex).

Out of a large pool of approximately 650 participants, we selected 38 healthy volunteers, who successfully fulfilled all criteria. According to their age, we generated two groups: the “young group” included 26 participants aged between 20 and 35 years (mean age (SE): 24.96 (0.58) years) and the “older group” comprised 12 participants aged between 55 and 75 years (mean age (SE): 63.58 (1.27) years). The two groups were matched for sex distribution within the groups, and did not differ according to sleep and wake times, BDI, ESSm and PSQI (**Table 1**). However, they differed in the BMI, the MEQ and the MCTQ, such that the older participants were more morning types and the young were more intermediate chronotypes.

Laboratory part

The study consisted of three segments [i.e. one control light (i.e. dim light) condition and two experimental light conditions] of a 40-h sleep deprivation protocol each, performed in a balanced cross over design, separated by at least 3 weeks of an intervening period. Each segment lasted 56-h, starting with a baseline night of 8-h (according to subject’s habitual sleep time), following by a 40-hour episode of scheduled wakefulness, and ended by an 8-h recovery night (according to subject’s habitual sleep time). Participants remained in individual windowless and sound-attenuated bedrooms, without any time-of-day information. The light treatment of each condition consisted of 40-h of light exposition starting at subject’s wake time,

with either (a) control dim light (DL: <8 lux), (b) standard white light (WL: 250 lux, 2800K) or (c) blue enriched white light (BL: 250 lux, 9000K), all illuminances were vertical illuminances at the eye position of the participant (**Figure 1**). Participants were asked to take part in at least two conditions (control condition and an experimental condition: BL-DL: five young (4m/1f) and one older (1m/0f) / WL-DL: six young (4m/2f) and two older (1m/1f)) and, if they wanted, were allowed to complete the third condition (experimental condition: BL-DL-WL: 15 young (7m/8f) and nine older (7m/2f)). All conditions were controlled with regard to light influence (no electronic devices producing light were allowed), caloric intake (standardized meals every two hours), and body posture (semi-recumbent position during scheduled wakefulness). Participant's movements were reduced to a minimum and they had to stand up for regularly scheduled computer tests (light screen < 10 lux) and bathroom visits. Social interaction for participants was restricted to the contact with examiners and study helpers.

Assessment of subjective sleepiness

Subjective sleepiness was assessed every hour upon awakening from scheduled sleep at usual sleep times, using the Karolinska Sleepiness Scale (KSS) (Akerstedt *et al.*, 1994).

Salivary melatonin and cortisol

Saliva samples were collected at regular intervals during wakefulness to assess melatonin and cortisol levels. Sampling rates dynamically changed with circadian phase, such that sampling frequency was decreased during the biological day when melatonin secretion is low (one sample every hour), and increased during the biological evening, night and early morning hours (one sample every 30 minutes) (Brzezinski, 1997). Salivary samples were immediately frozen and kept at -20°C until the melatonin and cortisol assays were conducted.

A direct double-antibody radioimmunoassay was used for the melatonin assay [validated by gas chromatography–mass spectroscopy with an analytical least detectable dose of 0.65 pg/mL; Bühlmann Laboratory, Schönenbuch, Switzerland; (Weber *et al.*, 1997)]. The minimum detectable dose of melatonin (analytical sensitivity) was determined to be 2 pg/mL.

Cortisol was measured by ALPCO (ALPCO Diagnostics, Salem, NH, USA), using a direct salivary enzyme-linked immunosorbent assay (ELISA) for quantitative determination of cortisol. The sensitivity was 1.0 ng/mL and the intra-assay coefficient of variances amounts to 10.3% for baseline values 6.6 ng/mL.

Skin temperature

Skin temperatures were recorded throughout the 56-h of the protocol at a rate of one sample per minute. Recording ended immediately after the recovery night. Skin temperatures were measured using wireless temperature sensors (DS1922L, Thermochron, iButtons®, Maxim Integrated Products, Sunnyvale, CA, USA; resolution 0.0625 °C; for validation, see (van Marken Lichtenbelt *et al.*, 2006). The iButtons® were fixed to the skin with thin, air-permeable adhesive surgical tape on 6 locations: both hands (ventral part of left and right wrist), both feet (inner part of left and right foot, just below the ankle bone) and left and right infraclavicular region. For the analysis, distal skin temperature (DT) was calculated by averaging the skin temperature of both hands and feet, and proximal skin temperature (PT) was calculated as the average temperature of the left and right infraclavicular region. The distal-to-proximal skin temperature gradient (DPG) was defined as the difference between the proximal and distal skin temperature (DT-PT).

Wrist activity

Rest–activity cycles were measured by wrist actimetry using the Actiwatch system (Cambridge Neurotechnology Ltd, UK). The participants wore the activity monitor on the wrist of the non-dominant hand for the 56-h of the study. Actimetry data were analysed by the Sleep and Activity Analysis Software 7.23V (Cambridge Neurotechnology Ltd, UK). To avoid device-related sensitivity differences, the activity data were normalized for each actiwatch and averaged per 3-h epochs.

Statistical analysis

For all analysis, if not stated otherwise, the statistical package SAS (version 9.1; SAS Institute, Cary, NC, USA) was used with a mixed-model analysis of variance for repeated measures (PROC MIXED) with within factors “age” (young [Y] versus older [O]), ‘‘light condition’’ (dim light [DL] versus blue enriched white light [BL] versus white

light [WL]) and ‘‘time-of-day’’ (all assessed time points) and two random factors “subject” and “order of the session”. In order to reduce short-term fluctuations and the number of time segments, continuously recorded data were averaged in 3-h blocks. Contrasts were assessed with the LSMEANS statement and p values were based on Kenward-Roger’s corrected degrees of freedom (Kenward & Roger, 1997).

All time course measures were expressed as elapsed time awake according to each participant wake time. The figures are plotted relative to elapsed time awake and the average time-of-day indication was also added for a better understanding. It was calculated relative to the mean of the participant’s usual wake-up time, as they did not have the same scheduled time. All analyses comprised 26 young and 12 older participants, except for the cortisol and temperature assessment where only 25 young were involved (one participant did not give enough saliva sample to assess cortisol profile, and the iButtons of another participant did not record the temperature during the study).

For the melatonin onset and offset (Mel-on and Mel-off) following exposure to either DL, WL or BL, the melatonin data were resampled every minute using linear interpolation and the analysis was based on the mid-range crossing (25% of the amplitude) of bimodal skewed baseline cosine function (Van Someren & Nagtegaal, 2007) fitted to the resampled data as in (Kolodyazhniy *et al.*, 2012). The midpoint time was also calculated as the average time between the Mel-on and Mel-off. Melatonin amplitude was defined as the difference of the peak level to baseline levels of the BSBCF curve, the area under the curve encompassed the region from the baseline to the peak and "COG” time means melatonin midpoint by centre of gravity of the fitted curve. For these analyses only 25 young were involved because some values were missing around the peak for one participant.

The difference of melatonin variation under BL and WL compared to DL was also assessed. This analysis was done over a 24-h melatonin profile, from 16:00h on the first day to16:00h on the second day after the sleep deprivation night.

RESULTS

Subjective sleepiness

The analysis comprised 12 older and 26 young participants. The time course of subjective sleepiness is illustrated for each light condition and age group separately

(**Figure 2**). A main effect of “age” was observed, such that the older participants felt less sleepy during sustained wakefulness (40h) compared to the young under all extended light exposure conditions (DL, WL and BL). Furthermore, the main effect of “light condition” revealed that, independent of age, participants perceived their sleepiness at a lower level under the different light conditions compared to the DL. The main effect of “time of day” and the interaction of “time of day x age” indicated the well know circadian and homeostatic regulation of subjective sleepiness during sustained wakefulness with different dynamics in young and older participants, independent of the light conditions. Such that the subjective sleepiness was lower in the older participants compared to the young between 0 and 24-h and between 32 and 40-h of elapsed time awake (“age x time of day”: $p<0.0001$).

Salivary Melatonin and Cortisol

The well-known circadian profile of melatonin secretion was conserved in both age groups under all the three light conditions. We found a main effect of “time of day” and “light condition”, as well as an interaction of “light condition x age”, “time of day x age” and “light condition x time of day” (**Table 2**). All these effect were most likely driven by the young, as we found no significant differences between the light conditions in the older (light effect in the older: $p=0.2949$) but significant melatonin suppression in the young (light effect in the young: $p<0.0001$) (**Figure 2**). Melatonin was suppressed under WL and BL from 14 to 18-h of elapsed time awake (e.g. 22:00 to 02:00 h) compared to DL and even more under BL than WL from 16 to 20-h of elapsed time awake (e.g. 00:00 to 04:00 h). *Post-hoc* comparisons yielded significant melatonin suppression under BL and WL compared to DL. However, we found a main effect of “Light” for the DLMO onset (**Table 3**) in both age groups, such that melatonin onset was delayed under BL and WL compared to DL in both age groups. No significant differences were found for the DLMO offset for any light treatment and age group (**Table 3**). A main effect of “Light” was also found for the area under the curve, such that it was greater in the young compared to the older under DL and smaller under BL and WL compared to DL in the young group only. Furthermore, the midpoint time and the COG time were significantly delayed under BL and WL compared to DL in the young (**Table 3**).

The difference of melatonin variation under light condition and control condition yielded a main effect of "Time of day" ($F_{12,708}$=11.08, p<0.0001), "Age x Time of day" ($F_{12,708}$=3.07, p=0.0003) and "Light Condition x Time of day" ($F_{12, 708}$=1.85, p=0.0378), such that WL and BL suppress more melatonin in the young compared to the older (**Figure 3**). While the light did not modified melatonin suppression in the older, melatonin suppression in the young is only visible in the first part of the night (e.g. 00:00 to 04:00 h) and more pronounced under BL compared to white light.

The cortisol profiles across 40-h of extended light exposure under sleep deprivation revealed a clear circadian secretion pattern for both age groups and all three light conditions (**Figure 2**). We found a main effect of "age", "time of day", "Light", "age x time of day" and "age x light" mostly driven by the BL exposure (**Table 2**). *Post-hoc* showed a significant increase in cortisol under BL compared to WL and DL in the older only. Cortisol profile did not show differences between young and older participants under DL and WL exposure; however, under BL exposure older participants had higher cortisol levels than the young.

Skin temperatures

The DT values showed maximal values during the subjective night and minimal values during the day. They decreased rapidly in the early morning and, conversely, rised rapidly during the subjective night for both age groups. Nevertheless the light treatment did not have the same effect according to the age (**Figure 4**). Indeed, a main effect of "Age", "Light", "Time of day" and the interaction "Light x Age" was found (**Table 2**), *posthoc* comparisons yielded a decrease in DT in the older compared to the young under DL and WL, and a slight decrease in DT under WL compared to DL in the young.

In contrast, the PT showed maximal values during the day and minimal values during the subjective night. A main effect of "Light", "Age" and "Time of day" was found (**Table 2, Figure 4**). *Posthoc* comparisons revealed a decrease of PT under WL in the young compared to DL as well as in the older compared to the young under DL and WL.

Concerning the DPG measures we saw the same profile as in the DT. A main effect of "time of day", "light" and the interaction "age x light" was found (**Table 2**, **Figure 4**). *Posthoc* analysis revealed an increase in DPG under BL compared to DL in the older

but not in the young participants and a decrease in DPG in the older compared to the young under DL.

Wrist activity

Actimetry revealed a main effect of "time of day" (**Table 2**) such that the activity was stable across the daytime and increased during the biological night (**Figure 2**). This pattern was observed in both age group and under all conditions. The significant effect of the interaction "light x age" showed that the light differentially affected young and older activity levels. *Posthoc* comparisons revealed an increase of activity under BL in the young compared to WL and a tendency to increase as compared to DL, while in the older a decrease is found under BL as compared to WL. Interestingly, the level of activity in the older did not differ compared to the level in the young under WL and DL but a significant decrease of activity was present in the older compared to the young under BL.

DISCUSSION

Our data indicate that moderate (i.e. 250 lux) white light or blue-enriched white light significantly impacts on sleepiness, melatonin and cortisol profile, skin temperatures and motor activity in an age-dependent manner in healthy volunteers.

Does extended light exposure modify circadian markers in the young?

Melatonin: Many studies have shown that bright light exposure suppressed or shifted melatonin concentration (Gordijn *et al.*, 1999; Brainard *et al.*, 2008; Chang *et al.*, 2012; Sahin *et al.*, 2014) and even more under light at short wavelength (Lockley *et al.*, 2003; Cajochen *et al.*, 2005; Chellappa *et al.*, 2011b; Gabel *et al.*, 2013; Ruger *et al.*, 2013), which are in line with the greater melatonin suppression that we found under BL in the young. This phenomenon can be explained by the higher irradiance and melanopic values in the short wavelength, since the melanopsin-containing intrinsic photosensitive retinal ganglion cells (ipRGCs) implicated in the non-image-forming pathway are mostly sensitive to this wavelength. These ipRGCs are connected to the SCN through a specialized non-image-forming retinohypothalamic tract. As the pineal gland (central site for melatonin production) received direct neuronal projections from the SCN (Tsai *et al.*, 2009), nocturnal melatonin secretion

would then be phase advanced as would be predicted by the classical phase response curve of light to the circadian system when the exposure occurs in the morning hours (Khalsa *et al.*, 2003). Conversely, we found an attenuation of the evening rise in melatonin under light exposure which can be explained by the evening light exposure. However, it did not lead to a phase delay, as people also received light during the phase advance portion of the PRC, such that this shift was not conserved regarding the melatonin offset. One explanation could be that a possible delay caused by the evening light exposure was counteracted by a "phase advance" in the early morning as study participants are continually exposed to light. Furthermore melatonin suppression in the young occurred only in the first half of the subjective night. Interestingly, in the second part of the night no melatonin suppression was observed anymore even if participants were exposed to light at 250 lux across the entire 40-h protocol. These results could go in the direction of the hypothetical principle based on two oscillators in the rodents circadian system proposed by Pittendrigh and Daan, some years ago (Pittendrigh & Daan, 1976) and demonstrated also in humans (Daan *et al.*, 2001; Wehr *et al.*, 2001). This model describes a morning oscillators (M) entrained by the dawn light signal and an evening oscillator (E) entrained by the dusk signal.

This "masking" effect was also present in the subjective sleepiness curves; participants were less sleepy in the evening according to the attenuation of the rise of melatonin and reached the same level as under DL in the morning when melatonin concentration was not shifted anymore due to the supposed phase advance. In accordance with previous studies who showed that melatonin initiates not only distal vasodilatation but also sleepiness, acting therefore as the hormonal trigger between body heat loss and induction of sleep in the evening (opening of the sleep gate) (Campbell & Broughton, 1994; Cajochen *et al.*, 1996; Cagnacci *et al.*, 1997; Cajochen *et al.*, 2003).

However, we could not observe such differences in the evening in the others variables.

Skin temperature: The second most extensively used marker rhythms in human circadian studies is the core body temperature (CBT); in this study we presented only the skin temperatures as they play a major role in the regulation of the endogenous

circadian CBT rhythm. We showed inverse and higher amplitude rhythm regarding the distal skin temperatures compared to a general CBT curve and a similar pattern for the proximal skin temperature with the same amplitude than the CBT, as already demonstrated in many others studies (Krauchi & Wirz-Justice, 1994; Krauchi *et al.*, 2006). This opposite circadian rhythm in distal and proximal skin temperature rhythms reflects the differences in thermophysiological regulatory mechanisms. There is now evidence, that a rostral projection from the circadian pacemaker to the preoptic areas serves the circadian modulation of CBT (Moore & Danchenko, 2002) and that all these autonomically regulated mechanisms of shell size occur through constriction or dilatation of blood vessels (arterioles and AVAs) in distal skin regions (Hales *et al.*, 1985). Indeed, when the arteriovenous anastomoses are open, blood goes rapidly from the core to the distal skin regions, leading to body heat loss and decrease in CBT. The distal-proximal skin temperature gradient (DPG) provides a selective measure of distal skin blood flow, and, hence, of efficient body heat loss via the extremities (Rubinstein & Sessler, 1990; Severens *et al.*, 2010). It has previously been shown that these modulations are associated with melatonin secretion onset (Krauchi, 2007; Lack *et al.*, 2008), such that melatonin selectively augments distal skin blood flow while leaving proximal skin blood flow and cerebral blood flow unaffected (van der Helm-van Mil *et al.*, 2003). Nevertheless we did not find such a correlation in our data when participants were exposed to light.

Cortisol: Some studies have already shown that the normal transition from sleep to wakefulness, as well as switching on the light in the morning, contribute to amplify the morning increase of cortisol secretion. Also, sleep deprivation increased cortisol levels (Leproult *et al.*, 1997; Chapotot *et al.*, 2001) and a bright light exposure on the rising and descending phases of the cortisol rhythm (i.e., when cortisol levels are high) decreased cortisol levels in humans, however no effect was found when light was administered at the end of the descending phase (Leproult *et al.*, 2001; Jung *et al.*, 2010), which supports the hypothesis that cortisol is more or less sensitive to light exposure depending on its circadian phase (Scheer & Buijs, 1999; Ruger *et al.*, 2006). While a light exposure at 10000lux decreases cortisol levels, others studies reported that a night and early morning light exposure between 20-h and 6-h, at 600 to 3000lux broad spectrum light (Petterborg *et al.*, 1991; Thalen *et al.*, 1997; Lavoie

et al., 2003) or extended nighttime light exposure between 18-h and 8-h at 100 or 1000 lux (Foret *et al.*, 1996) caused no change in cortisol levels, suggesting that the intensity of bright light may be important in determining the effects of light on cortisol levels, which could be consistent with the findings of intensity response curves for melatonin suppression (Zeitzer *et al.*, 2000) although the exact dose-relationship for light illuminance and cortisol changes is not yet known. Our data in the young participants are in part in accordance with these findings, such that a long term light exposure decreases cortisol levels under BL compared to DL and WL, and a 250 lux exposure was enough to see an effect.

Does extended light exposure have the same effect on circadian markers in the older as compared to young?

It has been shown that the density of the lens increases with ageing (Coren & Girgus, 1972; Xu *et al.*, 1997; Najjar *et al.*, 2014), causing an alteration in the spectral absorption, and that the lens darkens and develops a yellow pigmentation that further reduces light transmission to the retina (Sample *et al.*, 1988). Lens absorption is more pronounced for short wavelength light that is optimal for appropriate entrainment of the endogenous biological clock (Charman, 2003). As a result, the levels of light reaching the retina will be reduced, leading to less photic entrainment of the circadian clock which could explain some changes in our older volunteers, such as the lack of melatonin suppression observed in the older participants, even though we can see a small attenuation in the evening rise as in the young group. Furthermore, due to the loss in ganglion cells with age (Curcio & Drucker, 1993), it may be that the older need higher light intensities to achieve the same light response as the young. On the other hand, melatonin levels under dim light were already at a rather low level in the older, which is in accordance with other studies (Cajochen *et al.*, 2006; Birchler-Pedross *et al.*, 2009), thus, the intensity of the light exposure in this study may not have been strong enough to suppress melatonin concentration any further. Indeed, even though some recent studies did not show an age related effect on melatonin responses to different light intensities over 1000lux (Kripke *et al.*, 2007; Kim *et al.*, 2014), Duffy and colleagues showed (Duffy *et al.*, 2007) that light

exposure between 100 and 1000lux have a weaker effect on melatonin phase shift in the older participants compared to the young. Another explanation could be that melatonin cannot be more suppressed because the lowest threshold of secretion is already reached under dim light exposure.

Surprisingly we found an increase in cortisol levels in the older group under BL compared to WL and DL and compared to the young group under BL as well. These data can neither be explained by a higher stress during the study in the older participants as they were less tense and felt more comfortable and happy compared to the young (data not shown), nor by a greater activity as they moved less under BL compared to the young. So far, we do not have an explanation for this cortisol variation as it is the first time that people were exposed to a continuous light for 40-h. The only extended nighttime light exposure (from 22-h to 8-h) at 100 or 1000 lux reported no significant differences in cortisol profile (Foret *et al.*, 1996).

Additionally, we discovered that skin temperature was generally lower in the older compared to the young. One can argue that because older people accumulate more fat than the young, as shown by a higher BMI in the older, and that a high fat content creates an insulating barrier for conduction and exchange of heat (Chudecka *et al.*, 2014), they will exhibit decreased heat dissipation in proximal body areas. However, this should not result in change distal body areas, where we still observed lower skin temperature levels in the older compared to the young. Moreover, we found an increase in distal temperature under BL in the older with no change under WL compared to DL. This finding needs further investigation in order to understand the underlying mechanism also taking into account other variables implicated in human thermoregulation.

Age-dependent effect of light on activity

A higher BMI was also shown to be correlated with lower physical activity (Bond *et al.*, 2014), which is in line with our results presenting a global lower or equal activity in the older compared to the young. Nevertheless, we have no explanation for the age-dependent light effect on activity levels in our study.

However, the global shape of activity across all groups and conditions is in accordance with the circadian modulation of the other variables; the maximum of activity was reached at the maximum of cortisol levels (circadian cortisol peak), when

participants were most sleepy, in the descending phase of melatonin concentration. One explanation for this activity increase is a compensatory behaviour to possibly counteract circadian sleep promotion and high sleep pressure levels during this time window.

One limit of the study is that the gender effect should have been investigated to have more precision about these interindividual differences, as it was already shown that women respond with a greater impairment in wellbeing compared to men under high sleep pressure (Birchler-Pedross *et al.*, 2009). Unfortunately, because of a too low number of women in the older group, we could not do so.

CONCLUSION

To put this data in a nutshell, we saw that circadian variations of physiological variables were maintained after 40-h of extended wakefulness in both age groups independent of light treatments. Furthermore, even though the older felt less sleepy under control condition compared to the young, the light decrease the subjective sleepiness in both age group. In addition, all circadian physiology in the older were at a lower level compared to the young, leading to the hypothesis of a more arousal state across the study for the older. Even if both blue- and non-blue-enriched white light induced a decrease in subjective sleepiness in all participants, melatonin level was supressed in the young under both light conditions in the first part of the subjective night only. For both light conditions no melatonin suppression was observed within the older participant group. Further investigation needs to be done in order to understand the age-dependent light effect on cortisol level, skin temperature and wrist activity.

As typical daylight exposure outdoors is in the order of tens of thousands lux, artificial light exposure indoors is relatively modest and limited to a few hundred lux only. Therefore, people that depend on artificial light, such as night- or shift-workers, as well as elderly and nursing home residents, will suffer from lack of light, particularly in the winter months. Thus, the use of moderately bright light in night work, shift work settings and nursing home, where constant light levels are very common, may have differential effects on young and older people. Therefore, the light device and

intensity should be adapted depending on the targeted population. Furthermore, all concerns about light pollution nowadays should be taken with moderation in regard of the small effect on circadian markers.

ADDITIONNAL INFORMATION

Competing interests

Luc JM Schlangen is an employee of Royal Philips Electronics N.V., The Netherlands.

Author contributions

Conception and design of the experiments: CC, VAU, GV, SLJM

Collection, assembly, analysis and interpretation of data: GV, MM, RCF, VA, CC, KV

Drafting the article or revising it critically for important intellectual content: GV, CC, VAU, SLJM, KV

All authors approved the final version.

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LEGENDS

Figure 1:

Spectral composition (light wavelength by irradiance; W/m2-nm) of the (A) polychromatic white light and the (B) blue-enriched polychromatic white light.

Figure 2:

Time course of the (A) Karolinska Sleepiness Scale (KSS), the (B) melatonin profile, the (C) cortisol profile and the (D) activity in 26 young participants (left panel) and 12 older (right panel) under Dim light (black lines), White light (red lines) or Blue enriched white light (blue lines). Data are plotted as a mean for each 2-hours bin for the KSS score, the melatonin and cortisol profile and 3-hours bin for the temperature and the activity relative to elapsed time (h) after wake-up. The error bars represent the standard error of the mean.

Figure 3:

Time course of the variation of melatonin concentration between the light conditions and the DL. The horizontal black line represents the baseline under DL. The difference of melatonin variation between the BL and the DL is depicted in light blue in the young (solid line) and in dark blue in the older (dash line), and the variation between the WL and the DL is in red in the young (solid line) and in violet in the older (dash line).

Figure 4:

Time course of the (A) distal-to-proximal skin temperature gradient (DPG) the (B) proximal temperature and the (C) distal temperature in 26 young participants (left panel) and 12 older (right panel) under Dim light (black lines), White light (red lines) or Blue enriched white light (blue lines). Data are plotted as a mean for each 3-hours bin relative to elapsed time (h) after wake-up. The error bars represent the standard error of the mean.

Table 1: Characteristics of the group of participants

Table 2: Results of the analysis of the variance for different physiological variables and subjective sleepiness for the time course of the study. In bold results with $p<0.05$.

Table 3: Results of the analysis of the variance for different melatonin variables. In bold results with $p<0.05$.

Table 1:

	YOUNG Mean (SE)	OLDER Mean (SE)	*p*
N (m,f)	26 (15,11)	12 (9,3)	
Age (year)	24.96 (0.58)	63.58 (1.27)	**<0.0001**
Sleep time (h:min)	23:23 (00:06)	23:10 (00:09)	0.2419
Wake time (h:min)	07:23 (00:06)	07:10 (00:09)	0.2419
BDI	2 (0.44)	1.83 (0.56)	0.8261
ESS	5.37 (0.60)	4.23 (0.66)	0.2559
MEQ	54.34 (1.37)	63.42 (3.13)	**0.0037**
MCTQ	4.71 (0.16)	2.86 (0.44)	**<0.0001**
PSQI	3.32 (0.31)	3 (0.46)	0.5635
BMI (kg/m^2)	22.19 (0.49)	25.32 (0.73)	**0.0010**

BDI: Beck Depression Inventory; ESS: Epworth Sleepiness Scale; MEQ: Horne & Ostberg morningness eveningness Questionnaire; MCTQ: Munich Chronotype Questionnaire; PSQI: Pittsburg Sleep Quality Index; BMI: Body mass index

Analysis of variance							
Variable	Age	Light	Time of day	Age*Light	Age*Time	Light*Time	Light*Time*Age
KSS	**$F_{1,35.8}$=12.54, *p*=0.0011**	**$F_{2,1943}$=9.38, *p*<0.0001**	**$F_{20,1937}$=93.37, *p*<0.0001**	$F_{2,1943}$=1.48, *p*=0.2290	**$F_{20,1937}$=3.78, *p*<0.0001**	$F_{40,1937}$=0.57, *p*=0.9874	$F_{40,1937}$=0.53, *p*=0.9935
Melatonin	$F_{1,35.9}$=2.73, *p*=0.1070	**$F_{2,1943}$=14.20, *p*<0.0001**	**$F_{20,1926}$=106.22, *p*<0.0001**	**$F_{2,1943}$=5.16, *p*=0.0058**	**$F_{20,1926}$=2.42, *p*=0.0004**	**$F_{40,1926}$=2.21, *p*<0.0001**	$F_{40,1926}$=0.72, *p*=0.9007
Cortisol	**$F_{1,34.9}$=9.19, *p*=0.0046**	**$F_{2,1823}$=3.34, *p*=0.0357**	**$F_{20,1802}$=150.16, *p*<0.0001**	**$F_{2,1823}$=19.08, *p*<0.0001**	**$F_{20,1802}$=2.13, *p*=0.0026**	$F_{40,1802}$=0.64, *p*=0.9616	$F_{40,1802}$=0.88, *p*=0.6851
DPG	$F_{1,35.1}$=2.71, *p*=0.1088	**$F_{2,1189}$=15.85, *p*<0.0001**	**$F_{13,1183}$=94.22, *p*<0.0001**	**$F_{2,1189}$=9.79, *p*<0.0001**	$F_{13,1183}$=1.30, *p*=0.2075	$F_{26,1183}$=1.02, *p*=0.4328	$F_{26,1183}$=0.23, *p*=1.0000
Proximal temperature	**$F_{1,35.1}$=4.93, *p*=0.0330**	**$F_{2,1188}$=30.80, *p*<0.0001**	**$F_{13,1183}$=18.80, *p*<0.0001**	$F_{2,1188}$=1.72, *p*=0.1790	$F_{13,1183}$=0.67, *p*=0.7959	$F_{26,1183}$=0.45, *p*=0.9922	$F_{26,1183}$=0.18, *p*=1.0000
Distal temperature	**$F_{1,35.1}$=6.13, *p*=0.0183**	**$F_{2,1187}$=18.04, *p*<0.0001**	**$F_{13,1183}$=76.88, *p*<0.0001**	**$F_{2,1187}$=14.89, *p*<0.0001**	$F_{13,1183}$=1.56, *p*=0.0918	$F_{26,1183}$=0.64, *p*=0.9204	$F_{26,1183}$=0.23, *p*=1.0000
Wrist Activity	$F_{1,35.8}$=3.40, *p*=0.0735	$F_{2,1233}$=2.42, *p*=0.0896	**$F_{13,1224}$=14.88, *p*<0.0001**	**$F_{2,1233}$=37.02, *p*<0.0001**	$F_{13,1224}$=1.56, *p*=0.0904	$F_{26,1224}$=0.33, *p*=0.9994	$F_{26,1224}$=0.46, *p*=0.9909

KSS: Karolinska Sleepiness Scale; DPG: Distal Proximal Gradient;

Table 2

Variable	Exact values of the variables			Analysis of the variance		
	DL (Young/Older)	WL (Young/Older)	BL (Young/Older)	Light	Age	Light * Age
Mel-on (h:min ± h:min)	21:48 ± 00:12/ 22:10 ± 00:10	22:58 ± 00:11/ 22:54 ± 00:26	23:08 ± 00:20/ 22:40 ± 00:24	**$F_{2, 58.7}$ =17.11, p<0.0001**	$F_{1, 35.4}$=0.00, p=0.9801	$F_{2, 58.7}$ =1.46, p=0.2417
Mel-off (h:min ± h:min)	07:55 ± 00:15/ 07:53 ± 00:25	07:52 ± 00:15/ 07:42 ± 00:28	07:42 ± 00:10/ 07:42 ± 00:13	$F_{2,60}$ =0.31 p=0.7377	$F_{1,35.1}$=0.30, p=0.8647	$F_{2, 60}$ =0.01, p=0.9917
Midpoint (h:min ± h:min)	02:50 ± 00:13/ 03:01 ± 00:18	03:25 ± 00:11/ 03:17 ± 00:20	03:25 ± 00:12/ 03:11 ± 00:15	**$F_{2,58.1}$=4.91, P=0.0107**	$F_{1,35.3}$ =0.00, p=0.9469	$F_{2, 58.1}$ =0.66, p=0.5221
Amplitude (pg/ml)	17.23 ± 1.83/ 11.87 ± 2.07	14.29 ± 1.86/ 11.48 ± 2.40	12.32 ± 1.77/ 11.83 ± 2.09	$F_{2,57.5}$ =2.00, p=0.1446	$F_{1,35}$ =1.37, p=0.2505	$F_{2,57.5}$ =1.61, p=0.2079
AUC	5.47 ± 0.59/ 3.74 ± 0.65	4.04 ± 0.57/ 3.10 ± 0.68	3.25 ± 0.46/ 3.33 ± 0.62	**$F_{2,57}$ =8.49, p=0.0006**	$F_{1,34.8}$ =1.38, p=0.2475	$F_{2,57}$ =2.43, p=0.0974
COG (h:min ± h:min)	02:38 ± 00:13/ 02:56 ± 00:20	03:22 ± 00:12/ 03:17 ± 00:19	03:27 ± 00:12/ 03:11 ± 00:20	**$F_{2,58}$ =9.25, p=0.0003**	$F_{1,35.3}$ =0.00, p=0.9726	$F_{2, 58}$ =1.46, p=0.2416

Mel-on: melatonin onset; Mel-off: melatonin offset; AUC, area under the curve; COG: melatonin midpoint by centre of gravity of the fitted curve

Table 3

Figure 1

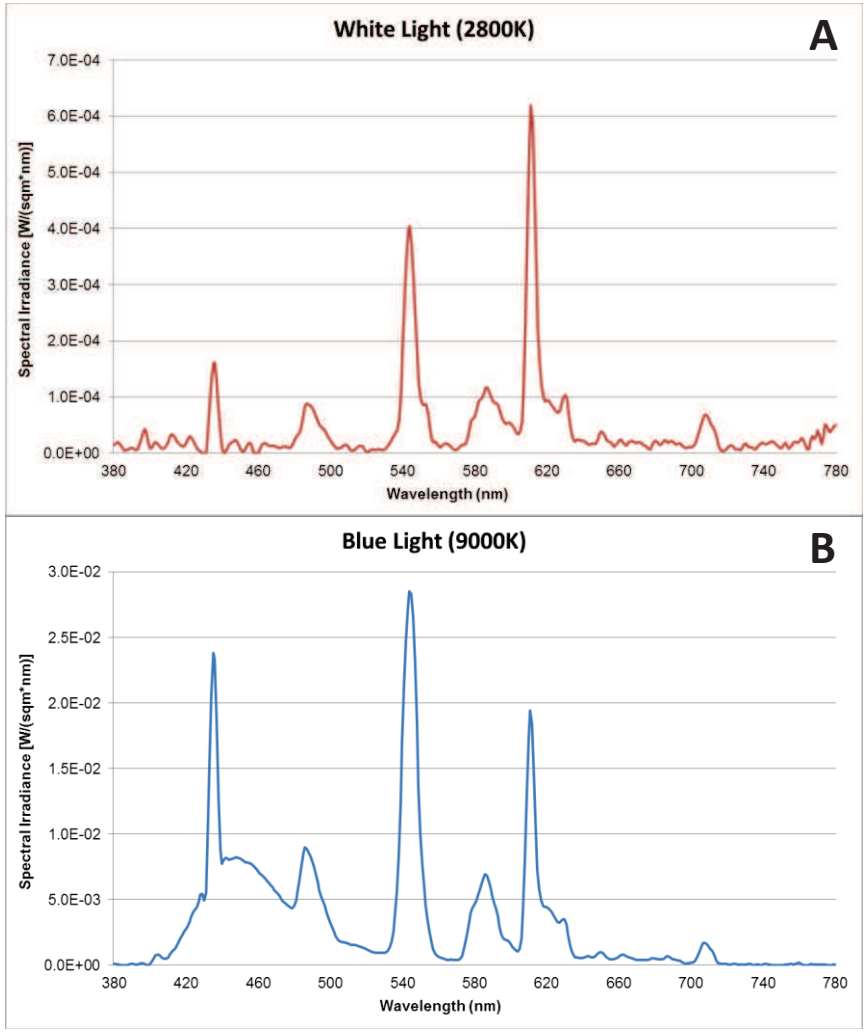

White Light (2800K)
A
Spectral Irradiance [W/(sqm*nm)]
7.0E-04
6.0E-04
5.0E-04
4.0E-04
3.0E-04
2.0E-04
1.0E-04
0.0E+00
380
420
460
500
540
580
620
660
700
740
780
Wavelength (nm)
Blue Light (9000K)
B
Spectral Irradiance [W/(sqm*nm)]
3.0E-02
2.5E-02
2.0E-02
1.5E-02
1.0E-02
5.0E-03
0.0E+00
380
420
460
500
540
580
620
660
700
740
780
Wavelength (nm)

Figure 2

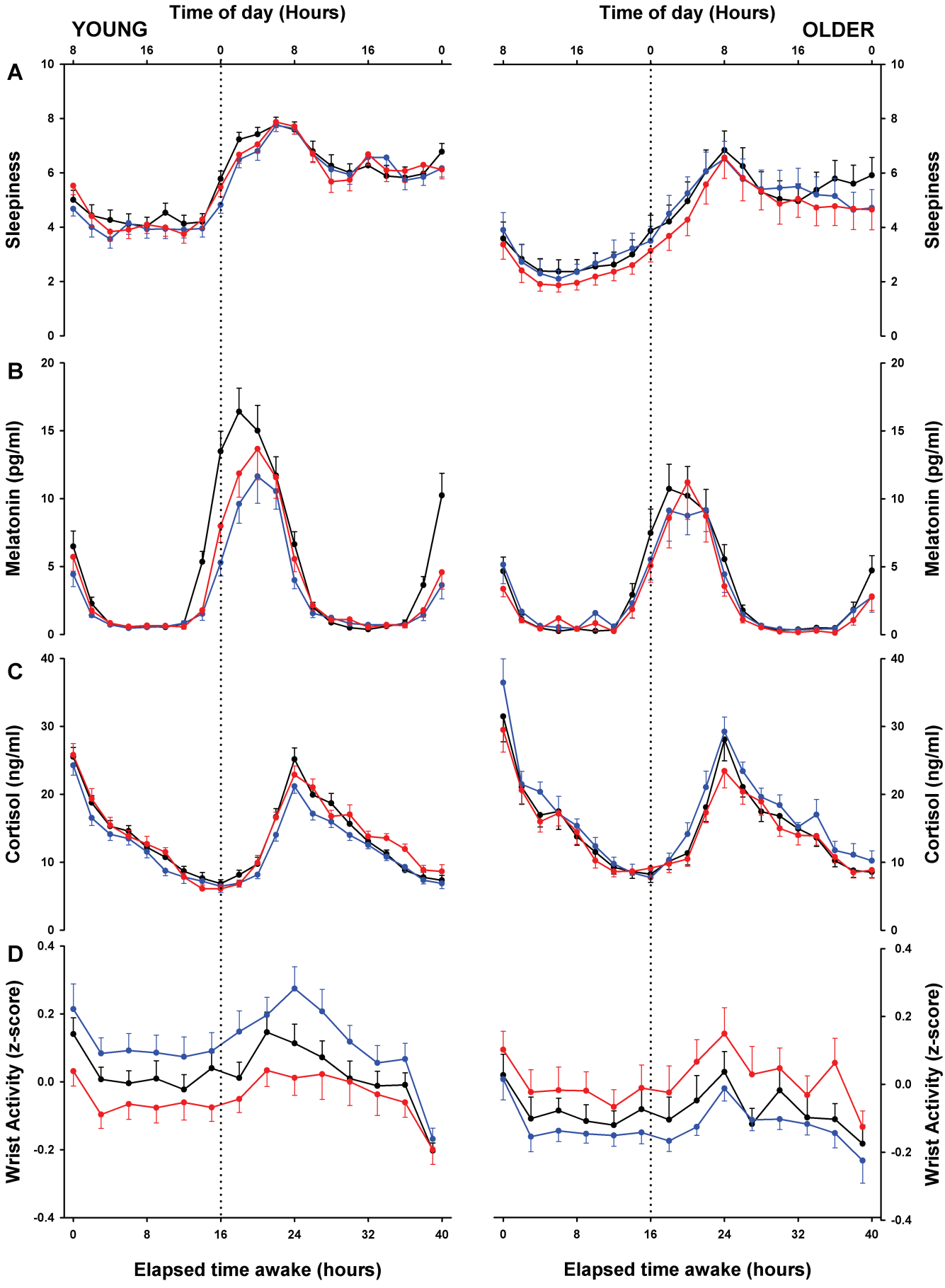

YOUNG
Time of day (Hours)
OLDER
Time of day (Hours)
A
B
C
D
Sleepiness
Melatonin (pg/ml)
Cortisol (ng/ml)
Wrist Activity (z-score)
Elapsed time awake (hours)
Elapsed time awake (hours)

Figure 3

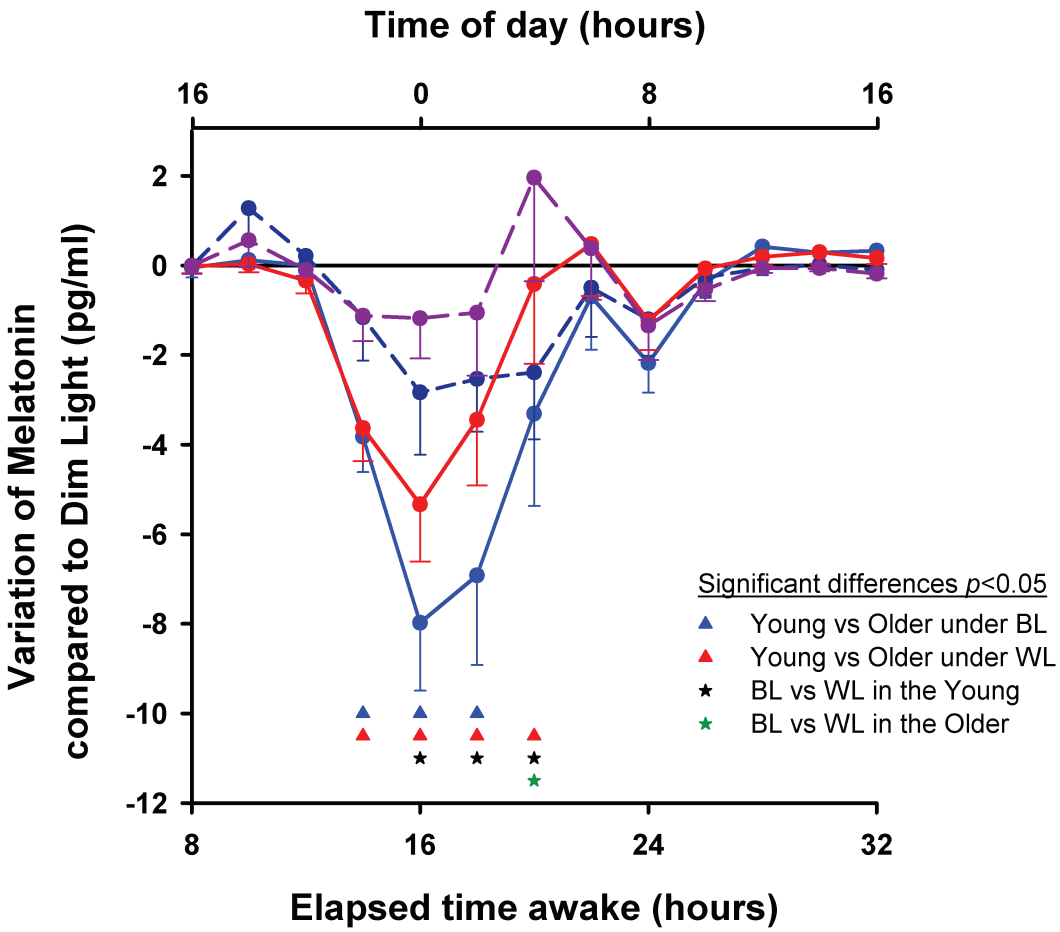
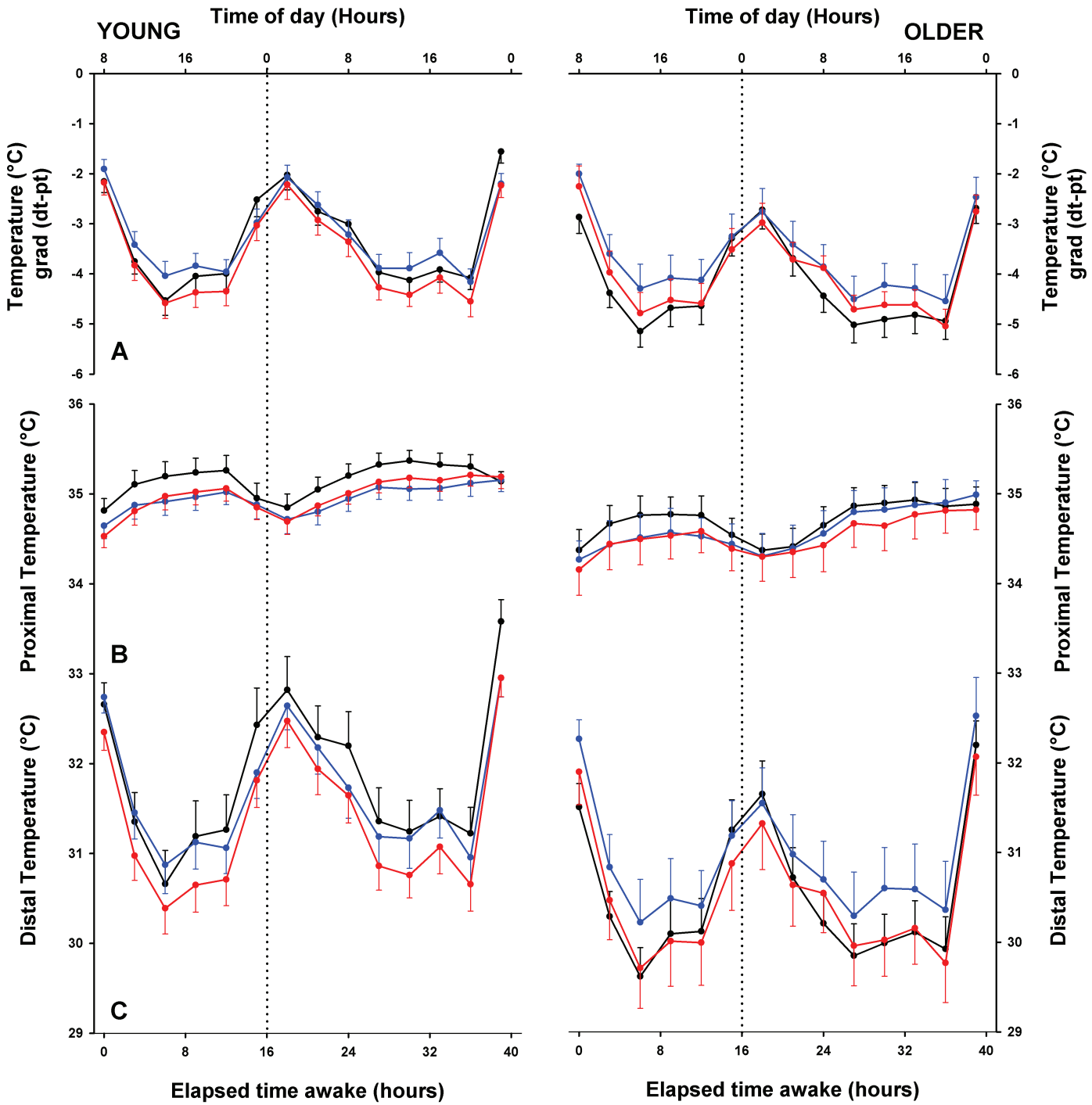

Time of day (hours)
16
0
8
16
2
0
-2
-4
-6
-8
-10
-12
Variation of Melatonin compared to Dim Light (pg/ml)
8
16
24
32
Elapsed time awake (hours)
Significant differences p<0.05
Young vs Older under BL
Young vs Older under WL
BL vs WL in the Young
BL vs WL in the Older

Figure 4


YOUNG
OLDER
Time of day (Hours)
Time of day (Hours)
8
16
0
8
16
0
Temperature (°C)
grad (dt-pt)
A
Proximal Temperature (°C)
B
Distal Temperature (°C)
C
0
-1
-2
-3
-4
-5
-6
36
35
34
33
32
31
30
29
0
8
16
24
32
40
Elapsed time awake (hours)
Elapsed time awake (hours)

V-Extended light exposure

2/ A genetic predisposition (i.e. PER3 polymorphism) and circadian physiology and cognition

Light effects depend on inter-individual differences: model of the *PER3* polymorphism.

Gabel V, Maire M, Reichert CF, Schmidt C, Cajochen C, Viola AU.

In prep.

Light effect on neurobehavioural and circadian physiological variables depend on inter-individual differences

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ABSTRACT

A polymorphism in the clock gene *PER3* has been shown to be related to neurobehavioural and endocrinological responses to sleep loss and light exposure. More specifically, homozygous carriers of the long allele repeat (*PER3*$^{5/5}$) are assumed to be more vulnerable to the detrimental effects of sleep loss and are more sensitive to blue-enriched light when applied in the evening than *PER3*$^{4/4}$ carriers. In this study we investigated whether an extended light exposure of moderately bright light at 250 lux for 40 hours can counteract a potential vulnerability to sleep loss in study volunteers carrying the *PER3*$^{5/5}$ when compared to *PER3*$^{4/4}$ carriers

Eight (6 men/ 2 women) homozygous long allele carriers (*PER3*$^{5/5}$: mean ± SE: 25.37 ± 1.10 years) and eight (6 men/ 2 women) homozygous short allele carriers (*PER3*$^{4/4}$: mean ± SE: 23.62 ± 0.42 years) underwent 40-hours of extended wakefulness once under dim light (DL: 8 lux), and once under either white light (WL: 250 lux) or blue-enriched white light (BL: 250 lux) exposure. Subjective sleepiness and well-being was assessed hourly along with melatonin and cortisol assays. A cognitive test battery was performed every 2.5-h.

Melatonin was significantly suppressed under both light conditions and in both genotypes, but with a significantly more pronounced effect under BL in the *PER3*$^{5/5}$. However, moderately bright light during 40 hours of sustained wakefulness induced a significant alerting response, better well-being and a decrease in cortisol levels only in the short allele carriers (*PER3*$^{4/4}$) under both light conditions. In contrast, the WL significantly decreased cognitive performance in the *PER3*$^{5/5}$ while it remained constant in *PER3*$^{4/4}$.

We have evidence for a clock gene genotype-related modulation of the non-visual response to light at 250 lux under extended wakefulness. However, a long term light exposure was not sufficient to counteract the assumed vulnerability to sleep loss from the *PER3*$^{5/5}$ carriers. In fact, we have evidence that such extended light exposure duration rather enhanced the detrimental effect of sleep loss seen in this genotype.

INTRODUCTION

Besides the major role of light in vision, more recently there is ample evidence that light also plays major role in regulating human circadian rhythms, subjective sleepiness and well-being, cognitive performances and physiology [1-5] more specifically at short wavelength [6, 7]. However, several inter-individual differences such as aging or a genetic predisposition in response to light have been reported [8-11].

Clock genes, such as the *PERIOD3* (*PER3*) genes, are deemed to play a pivotal role on these individual differences. For instance, the effects of the *PER3* polymorphism on cognitive brain responses to light, melatonin suppression, and subjective alerting response to light appear to be fairly substantial [10, 11]. This gene contains a primate-specific variable number tandem repeat (VNTR) polymorphism [12]; a 54 nucleotides unit repeated, in humans, four (short allele, $PER3^{4}$) or five (long allele, $PER3^{5}$) times [13, 14]. Studies showed that this polymorphism is related to diurnal preference and delayed-sleep-phase syndrome (DSPS) [14-16]. More recently, the homozygous carriers of the longer allele ($PER3^{5/5}$) have been shown to be more vulnerable to sleep loss compared to the homozygous carriers of the shorter allele ($PER3^{4/4}$) [17-19]. This vulnerability is also reflected in cognitive performance such that $PER3^{5/5}$ had higher cognitive impairment [20, 21]. Moreover, Chellappa and colleagues highlighted a genotype-dependent impact of light when administrated in the evening, such that the $PER3^{5/5}$ were more sensitive to blue-enriched light [10].

Here we aimed at investigating how physiological and behavioural variables can differ and can be potentially improved by different light exposure in humans with respect to their genetic predisposition (homozygosis in the clock gene polymorphism

(i.e. *PER3*)). Secondly, we tested for the first time whether an extended exposure to moderately bright light (250 lux) can improve vulnerability to sleep loss, particularly in *PER3*$^{5/5}$ carriers.

We predicted a greater suppression in melatonin and a decrease in cortisol levels under blue-enriched polychromatic light exposure, which is more prominent in *PER3*$^{5/5}$ individuals, since they may exhibit a higher sensitivity to these light-induced effects, in comparison to *PER3*$^{4/4}$. Morover, we expected a greater enhancement in alertness and cognitive performance under blue-enriched polychromatic light exposure which will be more prominent in volunteers carrying the *PER3*$^{5/5}$ polymorphism. This assumption is also based on the fact, as shown in our previous study [5], that volunteers who show lower performance benefit more from the light than high peformers. Thus, as *PER3*$^{5/5}$ carriers showed a larger deterioration in performance [21, 22], they may benefit more from this light-induced alerting effect on their deteriorated alertness and cognitive performance levels during sleep deprivation.

MATERIAL AND METHODS

Participants

All volunteers completed a consent form, a general medical questionnaire, the Beck Depression Inventory II (BDI-II) [23], the Epworth Sleepiness Scale (ESS) [24], the Horne Ostberg Morningness Eveningness Questionnaire (MEQ) [25], the Munich Chronotype Questionnaire (MCTQ) [26] and the Pittsburgh Sleep Quality Index (PSQI). The study protocol, screening questionnaires, and consent forms were approved by the local ethics committee (EKBB/Ethikkommission beider Basel, Switzerland), and conformed to the Declaration of Helsinki.

Participants did not suffer from any general medical, psychiatric and sleep disorders, and habitually slept between 7 and 9 h per night. PSQI values were requested to lie below 5 and BDI-II values below 12. Further exclusion criteria encompassed smoking, medication (except oral contraceptives), or drug consumption. To control for circadian phase misalignment, we excluded shift workers, and study applicants who had trans-meridian flights during three months before study participation. All women were tested for pregnancy prior study begins. They were required to participate during their luteal phase unless they were taking hormonal contraceptives.

Sixteen young healthy volunteers participated in the study. The distribution of Per3 genotype was eight homozygous carriers of the short repeat allele (*PER3*$^{4/4}$, 6 men and 2 women; mean age ± SD: 23.62 ± 0.42) and eight homozygous carriers of the long repeat allele (*PER3*$^{5/5}$, 6 men and 2 women; mean age ± SD: 25.37 ± 1.10). The volunteers were matched according to age, BMI and ethnicity and thus did not differ in terms of age, sleep and wake time, BDI, ESS, PSQI, and chronotype score (**Table 1**). To rule out sleep disturbances and to assess their ability to sleep in a new environment, participants slept one night at the Centre for Chronobiology prior to study begin. They also underwent a medical screening to guarantee physical and mental health, as well as an ophthalmologic examination in order to exclude volunteers with visual impairments (visual field, colour vision, pupillary reflex). One week before the study, participants were requested to refrain from alcohol, caffeine, and chocolate intake. They were also instructed to keep a regular sleep-wake schedule (bedtimes and wake times within 30 min of self-selected target times) for one week prior to each study segment. Compliance was verified by wrist actigraphy (Actiwatch L; Cambridge Neurotechnologies, Cambridge, UK) and self-reported sleep logs.

Laboratory part

A balanced crossover design study was conducted, which consisted of three segments of 56-h each, separated by an intervening period of at least 3 weeks. Each session comprised a baseline night and a recovery night of 8-h (according to the participants habitual sleep time) separated by 40-h of extended wakefulness (**Figure 1**). Participants remained in individual windowless and sound-attenuated bedrooms, without any time of day information and were exposed during their time awake to either (a) control dim light (DL: <8 lux), (b) standard white light (WL: 250 lux, 2800K) (**Figure 1A**) or (c) blue enriched white light (BL: 250 lux, 9000K) (**Figure 1B**). Participants were asked to complete at least two conditions (control condition and an experimental condition) and, if they wanted, were allowed to complete the third condition (experimental condition), the rates we obtained were equal for both genotypes [5 participants (4m/1f) underwent the three light conditions, 1 participant (0m/1f) underwent the DL and the BL condition and 2 participants (2m/0f) underwent the DL and the WL condition]. All conditions were controlled with regard to light influence (no electronic devices producing light were allowed), caloric intake (standardized meals every 2 h), and body posture (semi-recumbent position during scheduled wakefulness). Participant's movements were reduced to a minimum and they had to stand up for regularly scheduled computer tests and bathroom visits. Social interaction for participants was restricted to the contact with examiners and study helpers.

Genotyping

DNA was extracted from saliva samples collected with the Oragene┐ DNA Collection Kit using the standard procedures (DNA Genotek Inc., Ontario, Canada; http://www.dnagenotek. com/ROW/support/protocols.html). All genotypes were determined with an allele-specific PCR using Hot FIREPolDNApolymerase and a forward (50-TTA CAG GCA ACA ATG GCA GT-3') and reverse (50-CCA CTA CCT GAT GCT GCT GA-3') primer. The PCR products were analyzed by agarose gel (2%) electrophoresis to identified the genotype of he participants.

Assessment of subjective sleepiness and well-being

Subjective sleepiness was assessed every hour upon awakening from scheduled sleep, using the Karolinska Sleepiness Scale (KSS) [27]. Subjective well-being was assessed hourly with a Visual Analogue Scale (VAS) with a composite score calculated as follows, [VAS mood + (100 - VAS tension) + (100 - VAS physical comfort)] / 3, according to Birchler-Pedross and colleagues [28].

Salivary melatonin and cortisol

Saliva samples were collected throughout the entire 40-h of sleep deprivation to assess melatonin and cortisol levels. Sampling frequency was decreased during the biological day when melatonin secretion is low (one sample every hours), and increased during the biological evening, night and early morning hours (one sample every 30 minutes) [29] to detect a change in melatonin secretion. Salivary samples were immediately frozen and kept at -20°C until the melatonin and cortisol assays were conducted.

A direct double-antibody radioimmunoassay was used for the melatonin assay (validated by gas chromatography–mass spectroscopy with an analytical least detectable dose of 0.65 pm/mL; Bühlmann Laboratory, Schönenbuch, Switzerland; [30]). The minimum detectable dose of melatonin (analytical sensitivity) was determined to be 2 pg/mL.

Cortisol was measured by ALPCO (ALPCO Diagnostics, Salem, NH, USA), using a direct salivary enzyme-linked immunosorbent assay (ELISA) for quantitative determination of cortisol. The sensitivity was1.0 ng/mL and intra-assay coefficient of variances amounts to 10.3% for baseline values 6.6 ng/mL.

Cognitive performance

During the 40-h of wakefulness, participants completed a test battery every 2.5-h starting 30min after the wake-up time. The battery was composed of four cognitive tasks, including sustained attention (Sustained Attention to Response Task, SART [31]) and working memory (Verbal 1-, 2-, 3-back [32]). To assess the global level of light effect on cognitive performance, a composite score was computed by normalising the data for each test separately and averaging it to obtained a composite score for each participant for every 2.5-h period [4, 21].

Statistical analysis

Group analyses were performed with the statistical package SAS (version 9.1; SAS Institute, Cary, NC, USA). We used a mixed-model analysis of variance for repeated measures (PROC MIXED) with within factors “genotype” (*PER3*$^{4/4}$ versus *PER3*$^{5/5}$), ‘‘light condition’’ (dim light [DL] versus blue enriched white light [BL] versus white light

[WL]) and ‘‘time-of-day’’ (all assessed time points) and two random factor “subject” and “order of the condition”.

For the dim light melatonin onset and offset (Mel-on and Mel-off) following exposure to either DL, WL or BL, the melatonin data were resampled every minute using linear interpolation and the analysis was based on the mid-range crossing (25% of the amplitude) of bimodal skewed baseline cosine function [33] fitted to the resampled data as in [34]. The midpoint time was also calculated as the average time between the Mel-on and Mel-off. Melatonin amplitude was defined as the difference of the peak level to baseline levels of the BSBCF curve, the area under the curve encompassed the region from the baseline to the peak and "COG” time means melatonin midpoint by centre of gravity of the fitted curve.

RESULTS

Assessment of subjective sleepiness and well-being

The time course of subjective sleepiness is illustrated for each genotype and light separately (**Figure 2, top panel**). We found a main effect of “Light condition”, “Time of day” and the interaction “Light condition x genotype” (**Table 2**). Posthoc analysis revealed that the light did not signficantly affect subjective sleepiness levels of the *PER3*$^{5/5}$ carriers, however the *PER3*$^{4/4}$ carriers felt less sleepy under both BL and WL compared to DL and compared to the *PER3*$^{5/5}$ carriers under BL.

The well-being pattern displayed a circadian profile, as assessed by a main effect of “Time of day”. In general, *PER3*$^{5/5}$ participants felt better compared to *PER3*$^{4/4}$ participants during the entire study protocol (**Figure 2, bottom panel**), with a greater effect in the first day of the protocol, illustrated by the “Genotype x Time of day” interaction (**Table 2**). The significant interaction “Genotype x Light condition”

indicated that the *PER3*$^{4/4}$ carriers reported higher subjective well-being under BL and WL compared to DL whereas the *PER3*$^{5/5}$ carriers felt better only under BL, as revealed by the *posthoc* analysis.

Salivary Melatonin and Cortisol

Because two women (both *PER3*$^{4/4}$) had very high melatonin levels (>2 standard devation from the mean) we decided to exclude all women (i.e. two *PER3*$^{4/4}$ and two *PER3*$^{5/5}$ carriers) from further melatonin analyses. The well-known circadian profile of melatonin secretion was conserved in both genotypes under all the three light conditions (**Figure 3, top panel**). We found a main effect of "time of day" and "light condition", as well as an interaction of "light condition x time of day" (**Table 2**), but no effect of genotype or its interaction with light condition and time of day. The analysis of the evening melatonin onset yielded a main effect of "light condition", such that it was delayed under both light conditions, and even more under BL for the *PER3*$^{5/5}$ carriers compared to DL (*PER3*$^{4/4}$: DL 21:58 ± 00:33h, WL 23:46 ± 00:28h, BL 23:15 ± 00:15h / *PER3*$^{5/5}$: DL 21:36 ± 00:22h, WL 22:50 ± 00:15h, BL 00:06 ± 00:30h). However, no significant difference was found for the melatonin offset. While no significant differences were found for the amplitude, the area under the curve (AUC) was significantly decreased under BL in comparison to DL in the *PER3*$^{5/5}$ carriers (**Table 3**). The analysis of the melatonin midpoint and COG showed a main effect of "light condition" such that, under WL and BL, the melatonin midpoint and COG occurred later compared to DL for the *PER3*$^{5/5}$ carriers.

The cortisol profiles across 40-h of extended light exposure under sleep deprivation revealed a clear circadian secretion pattern for both age groups and all three light conditions (**Figure 3, bottom panel**). A main effect of "light condition", "Time of day"

and the interaction “genotype x light condition” was found (**Table 2**). *Posthoc* analysis revealed that both WL and BL decreased cortisol level in the *PER3*$^{4/4}$ carriers particulary under BL. Furthermore, we found a genotype effect under DL, indicating that the *PER3*$^{5/5}$ carriers had lower cortisol levels compared to the *PER3*$^{4/4}$ carriers, which was not maintained under WL or BL.

Cognitive performance

Analysis of the composite score of cognitive performance revealed a circadian pattern, such that performance was at a lower level in the early morning (**Figure 4**), as assessed by a main effect of “time of day”. We also found a significant effect of the interaction “genotype x light condition” (**Table 2**). *Posthoc* comparisons yielded a significant decrease in cognitive performance for the *PER3*$^{5/5}$ carriers under WL exposure compared to DL but no light effect was detected for the *PER3*$^{4/4}$ carriers.

DISCUSSION

Our results showed that 40-h of extended light exposure have a differential effect on healthy young voluneers genotyped for a polymorphism in the clock gene *PER3.*

It has been shown that *PER3*$^{5/5}$ carriers have a faster sleep pressure build-up [17-19, 21] during wakefulness and are more vulnerable to total sleep deprivation [20-22]. Interestingly, our data showed that the *PER3*$^{5/5}$ carriers subjectively felt better under 40 hours of sleep deprivation under both light conditions than the *PER3*$^{4/4}$ carriers, while no significant difference was found regarding subjective sleepiness under DL. In addition, no significant differences were found between the genotypes

for the overall melatonin profile throughout 40-h of sleep deprivation under DL, as it was showned in previous studies [21, 22].

Furthermore, based on the expected higher vulnerability to total sleep deprivation in *PER3*$^{5/5}$ carriers [21], we expected a genotype depend effect with respect to cognitive performance in favor for *PER3*$^{4/4}$ carriers during total sleep deprivation. However, we could not confirm that, since our data did not show significant differences between the genotypes under DL. This could be explained by the use of a composite score instead of separate analysis for each test. Indeed, previous studies showed controversial data depending on the cognitive domain of the test and the vulnerabilty of *PER3* genotype [19, 22, 35, 36]. The composite we used encompassed three working memory tests and one sustained attention task. In a privious study, we showed better performance in sustained attention performance assessed with the Psychomotor Vigilance Task for *PER3*$^{4/4}$ [22], however, others found no significant differences [19, 35, 36]. Furthermore, under partial sleep deprivation, Goel and colleagues found no significant differences between *PER3* genotype in working memory task [35], while the *PER3*$^{4/4}$ carriers performed better under partial sleep restriction with subsequent total SD [19] or under total sleep deprivation in a more demanding working memory task only [20]. Thus, there is evidence for a differential neurobehavioral sensitivity to sleep pressure relative to the *PER3* polymorphism. It would be relevant to further analyse each cognitive test according to the clock gene polymorphism (these data will be reported elsewhere).

Recently this polymorphism in the human clock gene *PER3* has been shown to play an important role in the light input of the circadian clock. A *PER3* knockout mice demonstrated a role for the gene in the light sensitivity of the non-classical photoreception system [37]. Furthermore, Chellappa and colleagues reported some

evidence for a differential non-visual response to light in long (*PER3*$^{5/5}$) and short (*PER3*$^{4/4}$) allele carriers [10]. Indeed, the homozygous carriers of the long allele exhibited a greater melatonin suppression and were less sleepy under a blue-enriched white light exposure compared to a white light, while no difference were shown for the homozygous carriers of the short repeat. These effects can be explained on one hand by the higher sensitivity to short wavelength from the melanopsin-containing intrinsic photosensitive retinal ganglion cells (ipRGC) [38-41]. Through their direct and indirect (via the suprachiasmatic nucleus) connections to subcortical and cortical networks, they will be responsible of the non-visual effect of light, and indirectly regulate the circardian rhythm [42]. On the other hand, Vandewalle and colleagues showed that blue light increased brain responses in a left thalamofrontoparietal circuit only in *PER3*$^{5/5}$ individuals when the sleep pressure was high.

Moreover, they revealed that the effects of light depend on circadian phase and homeostatic sleep pressure and also differ between the *PER3* genotypes, such that the most prominent effects were shown during the morning hours. They found similar significant effects of light but only in *PER3*$^{5/5}$ after a sleep deprivation night while only in *PER3*$^{4/4}$ after a normal night of sleep [11]. However, no effects were detected in both genotype in the evening after a normal waking day.

Next to these results, we were wondering whether a long term exposure can counteract the vulnerability to sleep loss of the *PER3*$^{5/5}$. Our data, however, suggest the opposite effect. Indeed, while the *PER3*$^{4/4}$ seemed to benefit more from the light, both white and blue-enriched white light did not increase subjective sleepiness or modifie cortisol profile in the *PER3*$^{5/5}$. In contrast, extended light expsoure led to decreased cognitive performance lelvels, particularly under WL. However, under BL,

cognitive performance were stable, the participant's well-being were enhanced and we also observed a greater melatonin suppression under BL in *PER3*$^{5/5}$ carriers, showing that the *PER3*$^{5/5}$ are more sensitive to BL, which corroborates previous results [10].

To conclude, even if the *PER3*$^{5/5}$ seemed to be more sensitive to BL compared to WL with respect to melatonin suppression, an extended light exposure had no beneficial effect on their neurobehavioral performance and on their cortisol profile. In contrast to our expectations, homozygous carriers of the short allele repeat, *PER3*$^{4/4}$, profited more from both light conditions across the 40-h of wakefulness.

Thus, a long term light exposure cannot counteract the assumed vulnerability to sleep loss, previously reported for *PER3*$^{5/5}$ carriers.

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LEGENDS

Figure 1:

Spectral composition (light wavelength by irradiance; W/m2-nm) of the (A) polychromatic white light and the (B) blue-enriched polychromatic white light.

Protocol design. Each session comprised a baseline night and a recovery night of 8-h (according to the participants habitual sleep time) separated by a 40-h of extended wakefulness. The stars represent the cognitive test battery assessed every 2.5 hours.

Figure 2:

Time course (left panel) and mean of all the time points (right panel) of the Karolinska Sleepiness Scale (KSS) (top panel)and the well-being (bottom panel) in 8 young participants *PER3*$^{4/4}$ and 8 *PER3*$^{5/5}$ under Dim light (black lines), White light (red lines) or Blue enriched white light (blue lines). Data are plotted as a mean for each 2-hours bin relative to elapsed time (h) after wake-up. The error bars represent the standard error of the mean. The horizontal lines on the right panel represent the significant difference between genotype and light condition.

Figure 3:

Top panel: Time course (left panel) and area under the curve (right panel) of melatonin profile in 6 young participants *PER3*$^{4/4}$ and 6 *PER3*$^{5/5}$ under Dim light (black lines), White light (red lines) or Blue enriched white light (blue lines).

Bottom panel: Time course (left panel) and mean of all the time points (right panel) of cortisol profile in 8 young participants *PER3*$^{4/4}$ and 8 *PER3*$^{5/5}$ under Dim light (black lines), White light (red lines) or Blue enriched white light (blue lines).

Data are plotted as a mean for each 2-hours bin relative to elapsed time (h) after wake-up. The error bars represent the standard error of the mean. The horizontal lines on the right panel represent the significant difference between genotype and light condition.

Figure 4:

Time course (left panel) and mean of all the time points (right panel) of the composite score of cognitive performance in 8 young participants *PER3*$^{4/4}$ and 8 *PER3*$^{5/5}$ under Dim light (black lines), White light (red lines) or Blue enriched white light (blue lines). Data are plotted as a mean for each 2.5-hours bin relative to elapsed time (h) after wake-up. The error bars represent the standard error of the mean. The horizontal lines on the right panel represent the significant difference between genotype and light condition.

Table 1: Characteristics of the group of participants

Table 2: Results of the analysis of the variance for subjective sleepiness and well-being, melatonin and cortisol profile and cognitive performance for the time course of the study. In bold results with $p<0.05$.

Table 3: Results of the analysis of the variance for different melatonin variables. In bold results with $p<0.05$.

Table 1:

	***PER3*$^{4/4}$ (mean ± SE)**	***PER3*$^{5/5}$ (mean ± SE)**	***p***
N (men,women)	8 (6,2)	8 (6,2)	
Age (years)	23.62 ± 0.42	25.37 ± 1.10	0.1597
Sleep time (h:min)	23:33 ± 00:06	23:22 ± 00:13	0.6420
Wake time (h:min)	07:33 ± 00:06	07:22 ± 00:13	0.6420
BDI	2.75 ± 0.65	1.37 ± 0.75	0.1884
ESS	6.25 ± 1.29	4.17 ± 0.33	0.1984
MEQ	53.00 ± 3.23	54.12 ± 1.99	0.7716
MCTQ	5.14 ± 0.26	4.48 ± 0.27	0.1056
PSQI	2.87 ± 0.35	3.50 ± 0.70	0.4416
BMI (kg/m^2)	20.90 ± 0.47	23.40 ± 0.75	**0.0138**

BDI: Beck Depression Inventory; ESS: Epworth Sleepiness Scale; MEQ: Horne & Ostberg Morningnes Eveningness Questionnaire; MCTQ: Munich Chronotype Questionnaire; PSQI: Pittsburg Sleep Quality Index; BMI: Body mass index

Analysis of variance							
Variable	Genotype	Light	Time of day	Genotype x Light	Genotype x Time	Light x Time	Light x Time x Genotype
KSS	**$F_{1,13.8}$=0.04, *p*=0.8373**	**$F_{2,745}$=5.18, *p*=0.0058**	**$F_{20,741}$=43.45, *p*<0.0001**	**$F_{2,745}$=5.10, *p*=0.0063**	$F_{20,741}$=0.73, *p*=0.7932	$F_{40,741}$=0.80, *p*=0.8017	$F_{40,741}$=0.56, *p*=0.9882
Well-being	$F_{1,14}$=0.81, *p*=0.3830	**$F_{2,743}$=19.99, *p*<0.0001**	**$F_{20,741}$=6.91, *p*<0.0001**	**$F_{2,743}$=5.94, *p*=0.0028**	**$F_{20,741}$=1.69, *p*=0.0302**	$F_{40,741}$=0.59, *p*=0.9804	$F_{40,741}$=0.34, *p*=1.0000
Melatonin	$F_{1,9.89}$=0.27, *p*=0.6176	**$F_{2,539}$=9.92, *p*<0.0001**	**$F_{20,536}$=38.54, *p*<0.0001**	$F_{2,539}$=1.81, *p*=0.1653	$F_{20,536}$=0.79, *p*=0.7299	**$F_{40,536}$=2.08, *p*=0.0002**	$F_{40,536}$=0.41, *p*=0.9995
Cortisol	$F_{1,13.1}$=0.02, *p*=0.8796	**$F_{2,685}$=6.96, *p*=0.0010**	**$F_{20,676}$=65.59, *p*<0.0001**	**$F_{2,685}$=23.30, *p*<0.0001**	$F_{20,676}$=1.15, *p*=0.2933	$F_{40,676}$=0.66, *p*=0.9498	$F_{40,676}$=0.75, *p*=0.8743
Cognitive performance	$F_{2,559}$=2.73, *p*=0.0658	$F_{1,14}$=1.24, *p*=0.2851	**$F_{15,555}$=13.32, *p*<0.0001**	**$F_{2,559}$=3.20, *p*=0.0416**	$F_{15,555}$=0.78, *p*=0.7036	$F_{30,555}$=1.02, *p*=0.4390	$F_{30,555}$=0.83, *p*=0.7336

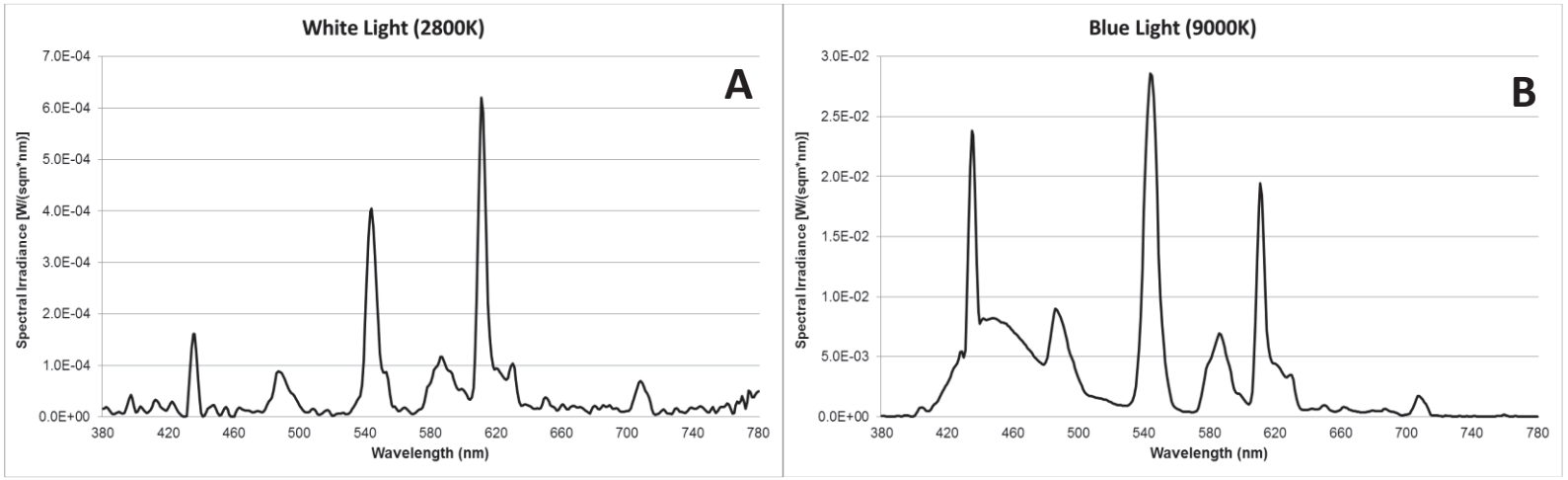
KSS: Karolinska Sleepiness Scale;

Table 2

	Analysis of the variance		
Variable	Light	Genotype	Genotype x Light
Mel-on	**$F_{2, 17}$ =17.54, p<0.0001**	$F_{1, 10.5}$=0.10, p=0.7535	$F_{2, 17}$=1.44, p=0.2638
Mel-off	$F_{2,16.3}$ =0.36, p=0.7010	$F_{1,9.75}$=0.82, p=0.3857	$F_{2,16.3}$=2.34, p=0.1282
Midpoint	**$F_{2,16.4}$=4.27, p=0.0321**	$F_{1,9.97}$ =0.54, p=0.4776	$F_{2,16.4}$ =1.11, p=0.3528
Amplitude	$F_{2,16.1}$ =0.86, p=0.4426	$F_{2,9.9}$ =0.02, p=0.8975	$F_{2,16.1}$ =0.12, p=0.8894
AUC	**$F_{2,16}$ =4.14, p=0.0357**	$F_{2,9.83}$ =0.06, p=0.8046	$F_{2,16}$ =0.16, p=0.8505
COG	**$F_{2,16.6}$ =8.48, p=0.0029**	$F_{1,10.1}$ =0.47, p=0.5105	$F_{2,16.6}$ =1.83, p=0.1920

Mel-on: melatonin onset; Mel-off: melatonin offset; AUC: area under the curve; COG: centre of gravity of the curve

Table 3


White Light (2800K)
A
Spectral Irradiance [W/(sqm*nm)]
7.0E-04
6.0E-04
5.0E-04
4.0E-04
3.0E-04
2.0E-04
1.0E-04
0.0E+00
380 420 460 500 540 580 620 660 700 740 780
Wavelength (nm)
Blue Light (9000K)
B
Spectral Irradiance [W/(sqm*nm)]
3.0E-02
2.5E-02
2.0E-02
1.5E-02
1.0E-02
5.0E-03
0.0E+00
380 420 460 500 540 580 620 660 700 740 780
Wavelength (nm)

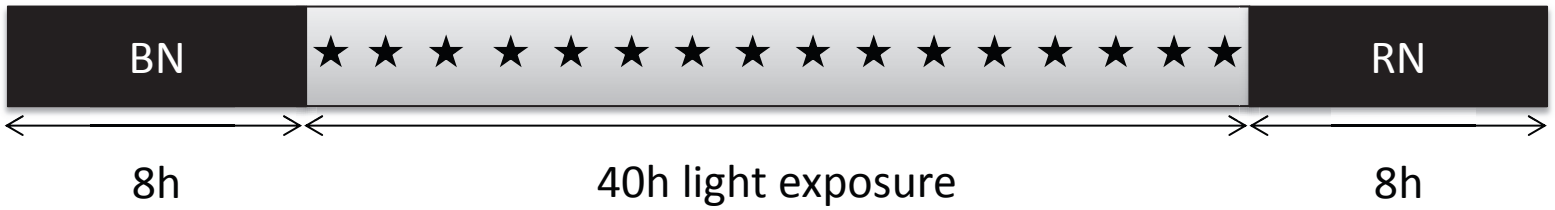

BN
RN
8h
40h light exposure
8h

Figure 2

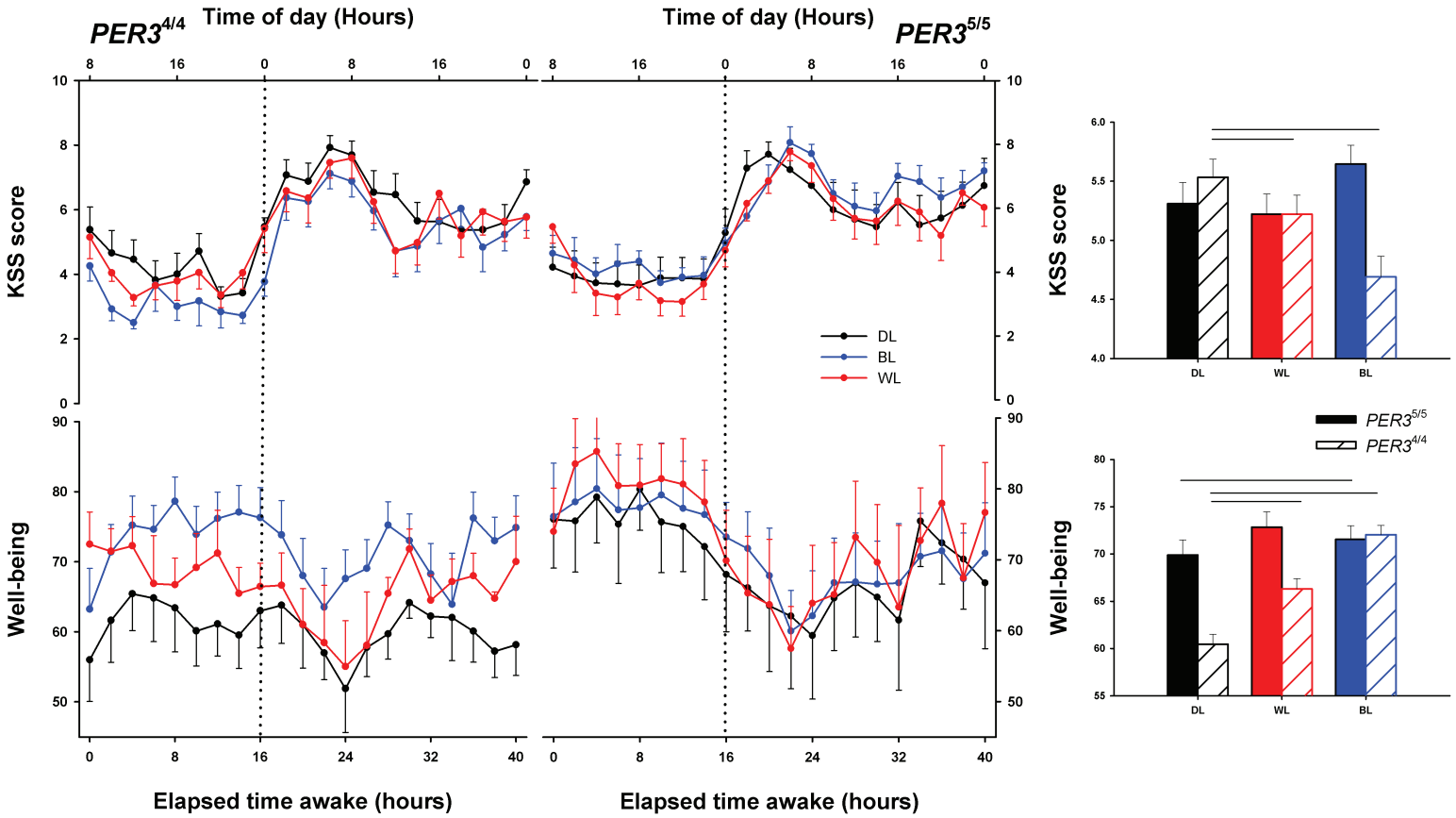

PER3 4/4
Time of day (Hours)
Time of day (Hours)
PER3 5/5
KSS score
Well-being
DL
BL
WL
Elapsed time awake (hours)
Elapsed time awake (hours)
KSS score
Well-being
PER3 5/5
PER3 4/4
DL
WL
BL

Figure 3

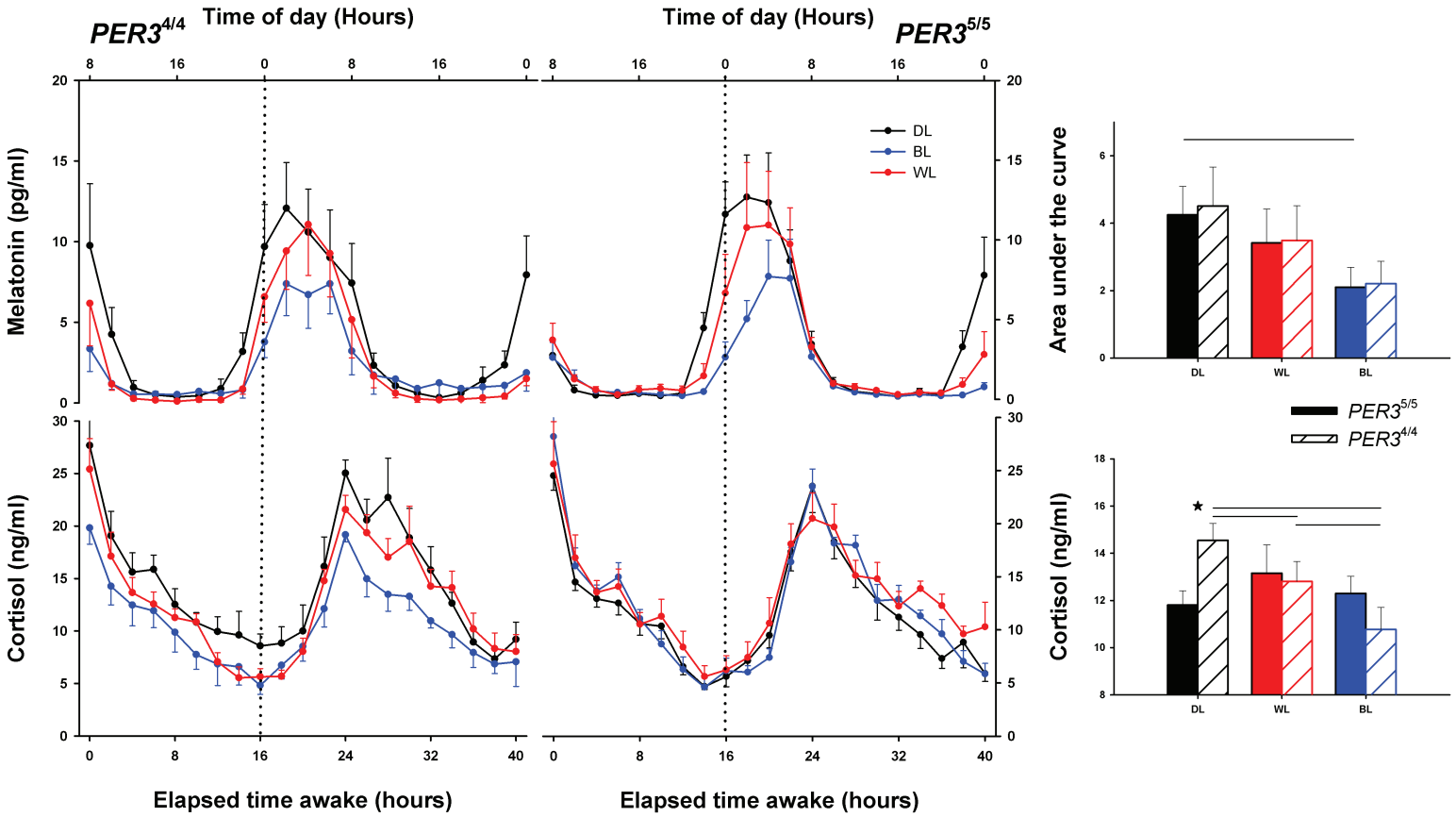
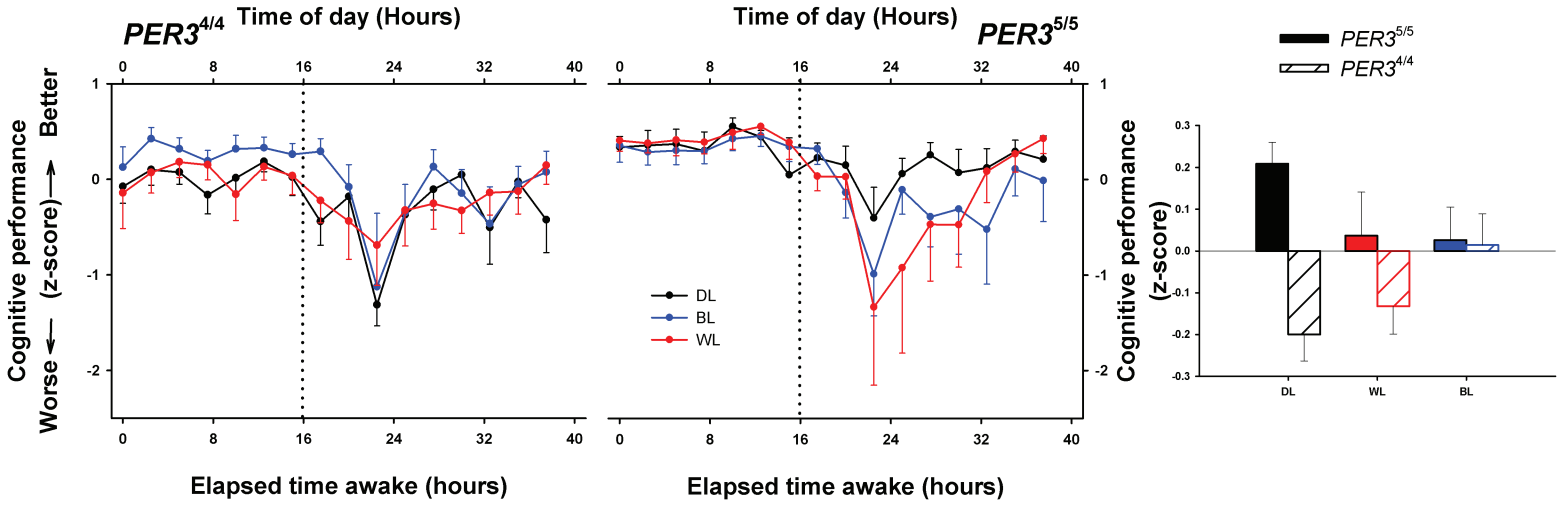

PER3^4/4
Time of day (Hours)
Time of day (Hours)
PER3^5/5
DL
BL
WL
Melatonin (pg/ml)
Cortisol (ng/ml)
Elapsed time awake (hours)
Elapsed time awake (hours)
Area under the curve
PER3^5/5
PER3^4/4
Cortisol (ng/ml)
DL
WL
BL

Figure 4


PER3^4/4
Time of day (Hours)
Time of day (Hours)
PER3^5/5
Cognitive performance
Worse ← (z-score) → Better
Elapsed time awake (hours)
Elapsed time awake (hours)
DL
BL
WL
PER3^5/5
PER3^4/4
Cognitive performance (z-score)
DL
WL
BL

VI- Discussion

This set of studies aimed at understanding how different light properties modulate human neurobehavioral performance and circadian physiology across the day, and how individual differences underscore the magnitude of these effects. Although we demonstrated that artificial dawn light exposure in the morning can counteract detrimental effects of sleep restriction (SR) on daytime cognitive performance, it does not necessarily imply that an extended light exposure further improves performance. Below, we discuss the pros and cons of these different light exposure regimes.

Can a morning light exposure counteract detrimental effects of sleep restriction on neurobehavioural and circadian physiological outcomes in young participants?

Chronic sleep restriction has deleterious effects on daytime subjective mood and cognitive performance [69, 71]. As light exposure has a beneficial effect on neurobehavioural variables and also affects hormones, such as melatonin and cortisol [4-7, 184] we wondered whether different morning light exposure modalities can counteract the detrimental effect of SR, by focusing firstly on the timing and dynamics of the light.

A 20-min morning monochromatic blue light exposure did not counteract the detrimental effect of SR (Chap. IV-1: [9]), even though it is known that the non-image forming action of light is blue shifted and thus more sensitive to short wavelength [5, 12, 122]. The duration of light exposure (20-min) was probably too short to elicit a significant long-term effect on neurobehavioural measures. Surprisingly, artificial dawn simulation light succesfully counteracted the detrimental effects of SR on cognitive performance, albeit not only in the first hours after awakening, as shown in previous studies [80, 189], but also for the remainder of the day, as indexed by increased subjective sleepiness, well-being, mood, relaxation, and global cognitive performance (chap. IV-1: [9]). The beneficial effect of the dawn simuation light depended on the cognitive domain of each test, as shown in our third paper (chap.

IV-2), such that it was most effective in attention-based tasks, motor-based skils and executive function.

Monochromatic blue light impacted on circadian rhythmicity, as indexed by a significant phase advance in melatonin and cortisol levels in the evening following light exposure (chap. IV-1), in line with previously observed phase advances for melatonin after intermittent blue light exposure [194]. However, the dawn simulation light did not affect circadian physiology, even though the rising phase of the dawn signal ended with blue-enriched white light. As the light started to progressively increase while participants were still asleep in the early morning, these dynamics of the light act more likely on the awakening and sleep inertia process than on the long-term modulation of circadian physiology. In fact, the dawn simulation light may facilitate the wake-up process by increasing cortisol levels immediately after wake-up (Chap. IV-1) and by reducing rapid wake-to-sleep evoked increases in heart rate and heart rate variability (chap. IV-1). Indeed, the observed gradient transition enveloping the wake-up process might have a protective effect for cardiovascular events, which usually peak in the early morning hours [88]. We showed for the first time that the dawn simulation light may “protect” the heart by an evolving preparation of cardiac physiology, thus, minimizing potential the cardiovascular vulnerability of wake-up process. The use of a dawn simulation light seems to be more appropriate to counteract the detrimental effect of SR compared to a morning monochromatic blue light exposure.

As a dawn simulation light can increase subjective sleepiness, well-being, mood, relaxation and global cognitive performance, we then focused on whether an extended light exposure can maintain similar effects as a morning light exposure, throughout the day, or if these effects are “weakened” in the course of a prolonged light exposure after reaching a “light threshold”.

Does a sustained 40-h exposure to light further improve and sustain sleepiness levels, and modulates circadian physiology?

In a second step, we focused more on the duration and the wavelength of light exposure.

Our results indicate that an extended exposure to moderately bright light (250 lux) did not sustain improved subjective sleepiness for the entire light exposure duration, but rather maintained its level independent on whether the light source is blue-enriched or not (chap.V-1). Thus, the light-induced improvement in sleepiness was not proportional to the duration of light exposure, but reached a threshold of effectiveness, which was also dependent on circadian phase, as assessed by the melatonin rhythm. In the same way, 40-h of light exposure did not enhance the phase and/or amplitude of markers of circadian physiology but, maintained them along the protocol. However, these effects were wavelength-dependent, as shown with differential changes in the cortisol profile, activity and skin temperature when using either a white or a blue-enriched white light (chap. V-1).

These wavelength-dependent effects, at least to some extent, were observed for the melatonin profile, but in a less pronounced manner. Even though an extended blue-enriched white light suppressed the melatonin profile, the suppression was also visible under an extended non-blue-enriched white light exposure in the young, similar to previous studies [5, 8, 9, 148, 195-200]. Furthermore, 40-h of light exposure did not significantly change circadian melatonin phase, but only attenuated the evening rise in melatonin levels. Contrariwise, its descending parts in the late night and early morning were not significantly affected. One explanation could be the counteracting effect of light which hit both the phase- advance and phase-delay portion of the phase response curve. Previous studies have raised the concept of two components of the circadian pacemaker [201-204], based on two oscillators in the rodent circadian system [205]. This model describes a morning oscillator (M) entrained by the dark-to-light transition and an evening oscillator (E) entrained by the light-to-dark transition. Accordingly, they observed that brief light pulses can reset the phase of offset of melatonin secretion without initially affecting the phase of onset [206, 207]. This concept may be congruent to our data, such that light in the morning

hours may reset the delayed melatonin phase which was induced by light exposure in the evening before.

While a dawn simulation light only increased cortisol levels immediately after wake-up (chap. IV-1), an extended blue-enriched light exposure of 250 lux decreased cortisol levels in the early morning hours in the young. These findings partly corroborate previous data showing that bright light exposure on the rising and descending phases of the cortisol rhythm decreased its levels [4, 208]. Nonetheless, extended white light did not exacerbate changes in cortisol profile as expected, probably because of the low intensity level. Indeed, some studies show that bright light exposure at 10000lux on the rising and descending phases of the cortisol rhythm decreases cortisol levels in humans, although no effects were described when light was administered at lower intensities [24, 209, 210] or at the end of the descending phase [4, 208].

Given that we only found an effect on cortisol level after a polychromatic blue-enriched white light exposure at 250 lux (Chap. V-1) and after a monochromatic blue light exposure at 100 lux (chap. IV-1), it might be assumed that the short wavelength is already efficient at a lower intensity levels, while the polychromatic white light might need to be at a higher intensity to be equally efficient. The most likely explanation may be that the intrinsic photosensitive retinal ganglion cells, responsible of the non-visual light effect, are most sensitive to the short wavelength. As they have direct and indirect (via the suprachiasmatic nucleus) connections to subcortical and cortical networks, they may regulate circadian rhythms with a more pronounced effect in light at short wavelengths [5, 198, 211]. Accordingly, an extended light exposure would not further enhance subjective sleepiness or modulate circadian physiology, but rather maintain them across the day.

How are individual differences, such as aging and a genetic predisposition, affected by this light?

A key finding (chap V) was that human responses to light show large inter-individual differences, such as a genetic predisposition (chap. V-2) (e.g. the polymorphism in the clock gene *PER3*) and aging (chap. V-1).

This specific polymorphism has been assumed to be related to diurnal preference [178, 212]. Moreover, homozygous carriers of the longer allele (*PER3*$^{5/5}$) seem to be more vulnerable to sleep loss compared to the homozygous carriers of the shorter allele (*PER3*$^{4/4}$) [66, 180, 213, 214]. Furthermore, it seems that *PER3*$^{5/5}$ carriers are more sensitive to light compared to *PER3*$^{4/4}$ carriers [21-23], thus indicating that differences in light sensitivity may be modulated by a clock gene polymorphism in the *PER3* gene.
In contrast to other studies [19, 180], we could not confirm greater vulnerability to 40-h sleep loss in *PER3*$^{5/5}$ compared to *PER3*$^{4/4}$ carriers. Furthermore, our extended light exposure of 250 lux could not successfully counteract sleep loss-related detrimental effects on cognitive performance. In fact, extended light exposure further worsened sleep loss-related performance changes in *PER3*$^{5/5}$ carriers, as indexed by decreased cognitive performance (chap V-2). Moreover, both light exposure settings did not increase performance in *PER3*$^{4/4}$, but maintained them at stable levels throughout the study protocol.

We confirmed earlier findings that older individuals had lower nocturnal melatonin levels than the young (chap V-1). Part of this age-related effect may be mediated by differences in their sensitivity to light [169-171] and a reduction of the amount of light input to the circadian clock [215]. Thus, it might be that older individuals need higher light intensities to achieve the same light response as for the young. Furthermore, possible rhythmicity disorders encountered in older people may be ascribed to a weakened oscillator [216, 217].

Conclusion and Outlook

We have evidence that a dawn simulation light in the morning can counteract the detrimental effects of sleep restriction and maintains its effects on neurobehavioral variables for the remainder of the day, with no impact on circadian physiology. In contrast, morning monochromatic blue-light exposure does not change neurobehavioral variables, but induces a phase-advance of the circadian melatonin and cortisol profiles. However, extended light exposure up to 40 hours does not further enhance neurobehavioral variables and circadian physiology, while it sustains its effect across the day in a wavelength-dependent manner. Thus, by manipulating the timing, duration, wavelength and dynamics of light exposure, it is possible to act more on neurobehavioral variables or on human circadian physiology. One should also take into account that light can also have deleterious effects when using inappropriate characteristics and depending on circadian rhythms and individual differences. For instance, we showed that an extended light exposure can attenuate the evening rise of melatonin, while other studies showed that circadian rhythms can be entrained to non-24-h day by evening bright light pulse [218]. Collectively these findings could be of great interest to treat circadian misalignment or circadian rhythm sleep disorders. However, light exposure in the evening can affect the sleep onset, quality and duration and can even become harmful for some people [156].

The dataset of this study also includes subjective mood, cognitive performance, blood pressure, heart rate, EEG patterns under extended light exposure, which still need to be analysed according to individual differences, such as age and a *PER3* genotype. As we showed that DsL impacts on cognitive performance in a domain-specific manner, it would be interesting to analyse whether both extended blue and non-blue enriched white light exposures mimic these domain-specific effects on cognitive performance to adapt the artificial daylight at home or in the office. In the same vein, the analysis of the effects of a 40-h sustained light exposure on HR and HRV may provide further information on circadian and sleep-dependent processes modulating cardiac activity, but could also explain the interpretation of our skin temperature profile data.

Moreover, we observed that individual differences, among them aging and the polymorphism in the clock gene *PER3*, differentially impact on the sensitivity to light. In this context, one should investigate whether morning light exposure has the same effects on these different groups and analyse more thoroughly a possible differential effect of the extended light exposure. Crucially, other types of individual differences, including gender, different gene polymorphisms (i.e. polymorphism of the clock gene ADA [219], and the combination thereof may also play a putative role in how individuals respond to light. Thereof, one could strategically adapt a light therapy according to these individual differences.

Furthermore, field studies should be designed to improve individual daily life, since dawn simulation light can enhance well-being, mood and performance during the following day and that a 40-h sustained light exposure at 250 lux also induces an improvement in subjective mood. Thus, it would be interesting to test if the combined use of a dawn simulation light followed by a bright light exposure during the day can further sustain the beneficial effect on subjective perception of well-being, sleepiness and mood as well as cognitive performance without impacting on key markers of the circadian system. This can be of great importance with respect to shift workers, who are exposed to sleep deprivation and chronic sleep restriction with a sleep/wake cycle shifted across the circadian timing system. Could a combined use of an extended light exposure during the night and a dawn simulation light after the “morning nap” help night-shift workers to alleviate decrements in cognitive performance and subjective mood during the day following their sleep deprivation night?

In a broader context, the work in this thesis shows that different light characteristics can be adapted according to each personal need. Dawn simulation light could be used after sleep restriction or sleep deprivation to enhance cognitive abilities during the following day or to improve fatigue, mood and well-being level before a good night of recovery. Using a bright light during the day may also help to improve subjective sleepiness, although it can also have deleterious effect on cognitive

performance. However, to resynchronize the body to the environmental rhythm (e.g. when traveling across different time zones), it would be best to recommend a monochromatic blue light pulse in the morning to phase-advance circadian rhythmicity or in the evening to phase-delay circadian rhythmicity.

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APPENDIX

Title: L'effet du simulateur d'aube sur notre organisme
The dawn simulation light effect on our organism

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MISE AU POINT

L'effet du simulateur d'aube sur notre organisme

The dawn simulation light effect on our organism

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MOTS CLÉS
Circadien ;
Comportement ;
Lumière simulatrice d'aube ;
Physiologie ;
Rythmes biologiques

Résumé Les rythmes biologiques sont d'une importance vitale pour l'être humain. Ils lui permettent d'anticiper les variations périodiques de l'environnement et d'assurer son homéostasie. Toutes ses activités métaboliques, physiologiques et cognitives sont gouvernées par des rythmes circadiens et réajustées chaque jour grâce à l'alternance jour/nuit. La lumière est le « donneur de temps » le plus puissant démontré jusqu'à aujourd'hui et permet de synchroniser l'organisme. Cependant, elle peut aussi être la cause de perturbations circadiennes si l'exposition ne se fait pas au moment propice de la journée. Les effets non visuels de la lumière ont été mis en évidence il y a quelques années seulement et font intervenir des récepteurs différents de ceux du système visuel. L'activation de ces récepteurs à certains moments de la journée entraîne une augmentation des performances cognitives, une amélioration de la vigilance et du bien-être et une modification du profil des marqueurs circadiens (mélatonine et cortisol). Récemment, il a été démontré qu'un réveil simulateur d'aube était bénéfique pour contrer les difficultés au moment du réveil au niveau physiologique et comportemental. De plus, les effets bénéfiques de ce simulateur se maintiennent tout au long de la journée et le rythme circadien n'est pas affecté. Ce réveil peut également être utilisé efficacement en luminothérapie pour traiter certaines maladies, comme les dépressions saisonnières, les démences, etc. Il pourrait ainsi être utilisé comme méthode non invasive pour contrer certains aléas de la vie quotidienne.

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Dawn simulation light;
Physiology

Summary Biological rhythms are vital for the human being. They allow to anticipate the periodic variations of the environment and to ensure homeostasis of the organism. All metabolic, physiological and cognitive activities are governed by circadian rhythms and reset every day through the light/dark cycle. Light is the strongest ''Zeitgeber'' to date and is responsible of the organism's synchronisation. However, it can also be the cause of circadian disruption if the exposure is not at the appropriate time of day. Non-visual effects of light have been discovered only a few years ago and involve different receptors apart from the visual system. Activation of these receptors at the appropriate time lead to an increase in cognitive performance, improvement in alertness and well-being and changes in circadian markers profiles (melatonin and cortisol). Recently, it has been shown that a dawn simulation light is beneficial to counter the difficulties upon awakening at physiological and behavioural level. Moreover, the beneficial effects of the light are maintained throughout the day and the circadian rhythm is not affected. This dawn simulation is also useful in therapy against diseases such as the seasonal depression, dementia, etc. It can thus be used as a non-invasive method to counter some difficulties of everyday life.

Le cycle veille/sommeil

La rythmicité est l'une des propriétés fondamentales du vivant. Toutes nos activités métaboliques, physiologiques et cognitives ont des rythmes circadiens (du latin circa, « environ », et diem, « jour ») permettant à l'organisme d'anticiper les variations périodiques de l'environnement et d'assurer ainsi son homéostasie. La réponse de l'horloge centrale à la lumière joue un rôle important dans la synchronisation des cycles environnementaux. Des études ont démontré qu'un pulse de lumière administré à différents moments de la journée entraînent un décalage de phase des rythmes circadiens. Plus précisément, une exposition à la lumière en soirée provoquera un retard dans l'apparition du sommeil alors qu'une exposition en matinée provoquera une avance de la phase d'endormissement [1]. Ces effets non visuels (NIF : *non image forming*) de la lumière sont donc nécessaires à la synchronisation entre le temps circadien interne et le temps externe (les 24 h de rotation de la terre). En conséquence, une atténuation du « Zeitgeber » ou sa survenue à un moment inapproprié peut entraîner une mauvaise synchronisation de ces deux entités.

L'entraînement des rythmes circadiens par la lumière se fait via des récepteurs spécifiques du système visuel, découverts dans les années 1990 [2,3], et différents des cônes et des bâtonnets. Ce sont les cellules ganglionnaires rétiniennes intrinsèquement photosensibles (ipRGC) [4—6], exprimant le photopigment mélanopsine. Ces cellules ont une sensibilité maximale dans les longueurs d'ondes courtes (460—480 nm) correspondant à la lumière bleue, contrairement à la sensibilité classique des récepteurs de la vision (< 550 nm) correspondant à une lumière verte [7—9]. Grâce au tractus rétinohypothalamique (RHT), elles transmettent les informations à différents noyaux hypothalamiques comme les noyaux suprachiasmatiques (*suprachiasmatic nucleus* [SCN]) qui représentent l'horloge centrale. À travers leur activité neuronale rythmique, les SCN permettent la synchronisation de l'ensemble du corps via des effecteurs spécifiques de l'horloge. L'hypothèse principale est que la mélatonine, hormone synthétisée par la glande pinéale et libérée de façon rythmique, serait l'effecteur essentiel pour cette homéostasie temporelle [1].

Cependant, les perturbations des rythmes circadiens sont de plus en plus observés dans notre société du fait des conditions de vie du monde moderne (travail de nuit, travail posté, nombreux voyages transméridiens) mais également du stress et du vieillissement général de la population. Ces perturbations favorisent la mise en place de pathologies à long terme, telles que troubles du sommeil, obésité, affections cardiovasculaires ou cancers, ainsi qu'à court terme, telle qu'une augmentation de la fatigue, une baisse de la vigilance et des performances cognitives ainsi qu'une modification de l'humeur. Il a été démontré qu'une exposition à la lumière vive non seulement stabilise le rythme de veille/sommeil mais aussi permet une meilleure synchronisation des rythmes circadiens et prévient des effets délétères du travail de nuit sur l'attention soutenue [10].

On observe également de grandes différences interindividuelles du cycle veille/sommeil. Ces différences font référence aux chronotypes qui peuvent être qualifiés de matinal, intermédiaire ou vespéral (du soir). De nos jours, le travail et les exigences sociales imposent des difficultés supplémentaires, notamment pour les chronotypes situés aux deux extrêmes [11]. Ce décalage entre le temps externe et interne est plus couramment appelé le « jetlag social ». Une des conséquences de ce décalage de phase est que les performances dans des tâches effectuées tôt dans la matinée sont diminuées chez les chronotypes du soir et inversement pour les chronotypes du matin.

Les chronotypes du soir présentent aussi une augmentation de la sévérité de l'inertie du sommeil. L'être humain souffre souvent de désorientation, de confusion et de fatigue pendant la période qui suit immédiatement la phase de réveil [12,13] et ses performances cognitives et physiques n'y sont pas optimales [14]. Cette inertie est présente à n'importe quelle heure du jour et de la nuit [15] et après différentes durées de sommeil [16,17]. Elle est la plus importante immédiatement après le réveil [18] et se dissipe progressivement, de sorte qu'au bout d'une heure, la fatigue subjective ainsi que les performances cognitives

s'améliorent significativement [16]. Le manque de lumière pendant la période hivernale peut également entraîner une aggravation de l'inertie du sommeil du fait de l'absence du stimulus d'avance de phase de la lumière matinale [19—21] et du manque de ses effets stimulants [22—24]. Il est donc d'un grand intérêt de comprendre les processus impliqués dans le phénomène d'inertie du sommeil et de valider des méthodes permettant de la réduire.

Les effets de la lumière

La lumière agit à différents niveaux et de manière spécifique. Elle agit sur le comportement en améliorant ou détériorant le niveau de bien-être, l'humeur, la vigilance, la fatigue et les performances cognitives, et aussi sur la physiologie en augmentant ou diminuant la température corporelle, en modulant la concentration de la mélatonine ou du cortisol et en provoquant un décalage de phase.

Elle se caractérise par la durée, le moment, la longueur d'onde et l'intensité de l'exposition. Plusieurs études ont mis en évidence que des modifications physiologiques et comportementales sont observables dès une exposition à 150 lux et que la suppression de la mélatonine, l'augmentation de la vigilance et de la température corporelle ainsi que du rythme cardiaque seront beaucoup plus sensibles à une lumière de longueur d'onde courte (dans le bleu) qu'à une lumière de longueur d'onde plus importante (dans le vert) pour laquelle les effets seront quasi-inexistants [7,25].

Il a récemment été découvert que la dynamique de la lumière, c'est-à-dire la façon dont l'exposition commence, entrait également en jeu dans les différentes réponses qu'elle induisait. Généralement, la lumière est allumée directement et augmente ainsi de plusieurs lux dans un temps très bref. Mais il existe à présent un type de lampes, le simulateur d'aube, dont l'intensité lumineuse augmente progressivement pendant un temps donné, puis se stabilise au niveau voulu (Fig. 1). Jusqu'à ce jour, ce dispositif n'a été testé qu'au moment de la transition sommeil/éveil. Ainsi, pendant les 30 minutes avant l'heure programmée du réveil, la personne étant encore endormie, l'intensité lumineuse augmente progressivement jusqu'à atteindre sa valeur maximale au moment où le réveil retentit. Cette dynamique simule ainsi le lever du soleil.

Ce sont les effets de ce simulateur d'aube que nous allons décrire ci-après.

Effet du simulateur d'aube

Sur l'inertie du sommeil

Si la lumière d'aube artificielle n'interagit pas nécessairement avec le système circadien, elle a des effets à court terme sur les variables physiologiques lors de la phase de réveil. En effet, certaines de ces variables, comme les changements de la circulation sanguine ou de la température de la peau suivent le processus d'inertie du sommeil. Une accélération de la baisse de température cutanée après le réveil a pu être observée suite à l'utilisation de la lumière d'aube artificielle, en comparaison avec un réveil brusque *On/Off* [26]. Ce phénomène pourrait être dû à l'activation directe du système nerveux sympathique par la lumière.

De même, lorsque la lumière d'aube artificielle commence à augmenter en intensité, les stades de sommeil se trouvent modifiés par rapport à un réveil normal sans aube artificielle. Environ 10 minutes après que le dispositif se soit mis en fonctionnement, quand l'intensité commence à croître, on observe une augmentation du nombre de micro-éveils. Bien que l'on ne sache pas si la personne est consciente de la luminosité présente dans la pièce, on peut penser que ces micro-éveils représentent un réveil progressif qui, contrairement au réveil brusque, pourrait avoir un effet positif sur l'inertie de sommeil.

Des chercheurs ont ainsi pu mettre en évidence qu'une exposition à une lumière d'aube artificielle 30 minutes avant que l'alarme du réveil ne retentisse, contrairement à un réveil effectué dans l'obscurité, entraîne une diminution de l'inertie du sommeil et augmente le bien-être général [27]. Elle induit également une amélioration des performances cognitives et physiques ainsi qu'une diminution du temps de réaction aux tests lors des 80 premières minutes après le réveil [28]. En accord avec ces résultats, une autre équipe a démontré que l'exposition à une lumière d'aube artificielle rendait les personnes moins fatiguées et plus actives pendant les 90 premières minutes qui suivent le réveil. Toutefois, ces effets ne s'observent pas lors des premières minutes suivant le réveil [26].

Le caractère progressif du réveil induit par le simulateur d'aube pourrait expliquer ces résultats sur les fonctions cognitives, notamment du fait que l'augmentation graduelle de la lumière permet une sécrétion accrue du cortisol au réveil [26,29], ce qui facilite une meilleure réactivité cérébrale.

Il est à noter que l'intensité finale de la lumière d'aube influence seulement la durée de l'inertie du sommeil : plus l'intensité de la lumière est élevée, plus l'inertie du sommeil se dissipe rapidement, alors que la fatigue subjective, le bien-être ou les performances cognitives restent stables quelle que soit l'intensité choisie.

Il a aussi été mis en évidence qu'un simulateur d'aube était plus efficace qu'un stimulus de lumière vive au réveil pour le traitement des patients souffrant de désordres affectifs saisonniers (SAD) [30,31].

Cela montre bien que l'exposition à la lumière avant le réveil exerce des effets bénéfiques pour contrer les difficultés rencontrées lors du réveil et que ces effets ne peuvent pas être atteints avec une exposition à une lumière vive postérieure au lever.

Tout au long de la journée

À côté de ces effets à court terme, la lumière simulatrice d'aube a également des effets à long terme. Nous avons pu démontrer que l'utilisation d'une lumière d'aube artificielle pour le réveil permettait d'améliorer la fatigue subjective, la tension, l'humeur et le bien-être ainsi que les performances cognitives tout au long de la journée (Fig. 2).

Bien que cette lumière améliore ainsi le comportement, elle n'en change pas pour autant le rythme interne (pas de différence dans la sécrétion de mélatonine), ce qui est d'autant plus avantageux [29]. En effet, nous avons vu plus haut que certaines expositions à la lumière provoquaient un décalage de phase. Or, si le but est d'améliorer les capacités

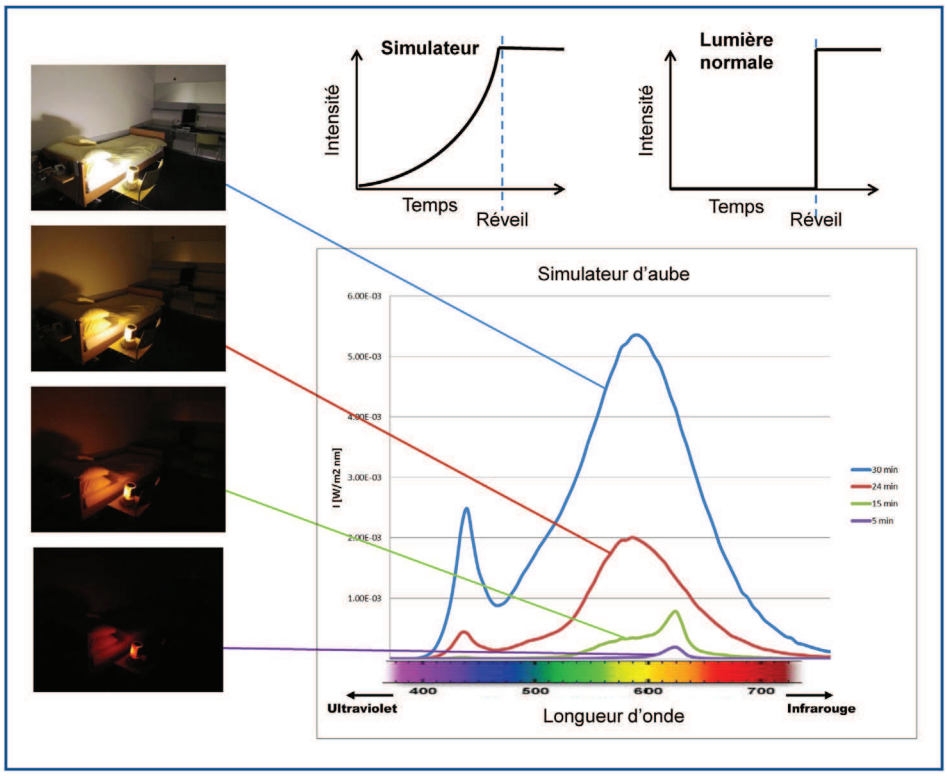

Figure 1. Dynamique de la lumière. Comparaison de la dynamique de la lumière d'un simulateur d'aube et d'une lumière *On*/*Off* normale. Composition spectrale du simulateur d'aube (irradiance de la lumière [W/m2-nm] en fonction de sa longueur d'onde) à 5 min (violet), 15 min (vert), 24 min (rouge) et 30 min (bleu).

ou de réduire la fatigue, il est préférable que l'horloge interne ne soit pas modifiée.

Néanmoins, les effets de la lumière simulatrice d'aube varient en fonction des tâches que la personne aura à accomplir et, en particulier, de l'importance des charges cognitives impliquées dans chacune de ces tâches. De manière générale, elle augmente les performances dans les tests d'attention, dans les tâches impliquant le système moteur et dans celles impliquant les fonctions exécutives, et améliore dans un même temps le temps de réaction lors de ces différents tests [32].

Ces effets s'expliquent par le fait que la lumière modifie l'activité des structures sous-corticales impliquées dans la vigilance, stimulant ainsi les fonctions cérébrales cognitives. Une des principales régions cérébrales engagées est l'hypothalamus antérieur, qui contient le noyau suprachiasmatique (SCN) et le noyau ventrolatéral pré-optique (VLPO) [33], formant le premier lien entre la rétine et le cerveau. De plus, plusieurs projections rétiniennes atteignent le noyau géniculé latéral (LGN) et le colliculus supérieur (SC). Le LGN se projette à son tour sur le cortex visuel primaire (V1), premier site de traitement visuel sensoriel, par une voie dorsale et une voie ventrale [12]. La voie dorsale est associée au traitement du mouvement (cortex médiotemporal, supérieur temporal et pariétal) alors que la voie ventrale est impliquée dans le traitement de l'information visuelle [13]. Par ailleurs, les effets modulateurs liés à l'attention affectent les deux voies : dans la voie dorsale, l'attention est encodée par des neurones impliqués dans l'attention spatiale comme l'orientation d'un objet ou un point en mouvement. En parallèle, les régions temporales supérieures et médiales ainsi que les régions corticales supérieures comme le cortex intrapariétal sont également impliquées dans ce processus [34]. La lumière joue ainsi un rôle modulateur dans les tâches d'attention spatiale.

Concernant la voie ventrale, la structure clé engagée dans l'attention est le SC, en collaboration avec les régions intrapariétales et le cortex visuel avec des connexions directes ou indirectes via le pulvinar (noyau thalamique dorsal) [14]. Ce dernier est essentiel dans la modulation de l'attention, il reçoit des projections rétiniennes directes et fournit un lien indirect entre les SCN et le cortex préfrontal [35]. Ainsi, il sert de médiateur dans la régulation de l'éveil. Les effets de la lumière sur le thalamus résulteront donc en une activation corticale généralisée, permettant la modulation des performances cognitives.

Mais la lumière a aussi des effets sur les fonctions exécutives, impliquant le cortex pariétal postérieur, le cortex prémoteur, le cortex préfrontal dorsolatéral (DLPFC) et le cortex préfrontal ventrolatéral (VLPFC) [36].

Par ailleurs, lorsque l'on compare deux groupes de personnes avec des niveaux de performance de base différents, on constate que la lumière simulatrice d'aube engendre une plus grande augmentation de ces performances dans le groupe des plus « faibles » que dans le groupe des plus « forts ». De sorte que les effets de cette lumière apparaissent plus bénéfiques aux personnes ayant de plus grandes difficultés au niveau cognitif comparées à celles ayant déjà un bon niveau de base [32].

Ceci montre que les effets de la lumière dépendent du domaine cognitif impliqué et diffèrent selon les performances basales de chacun.

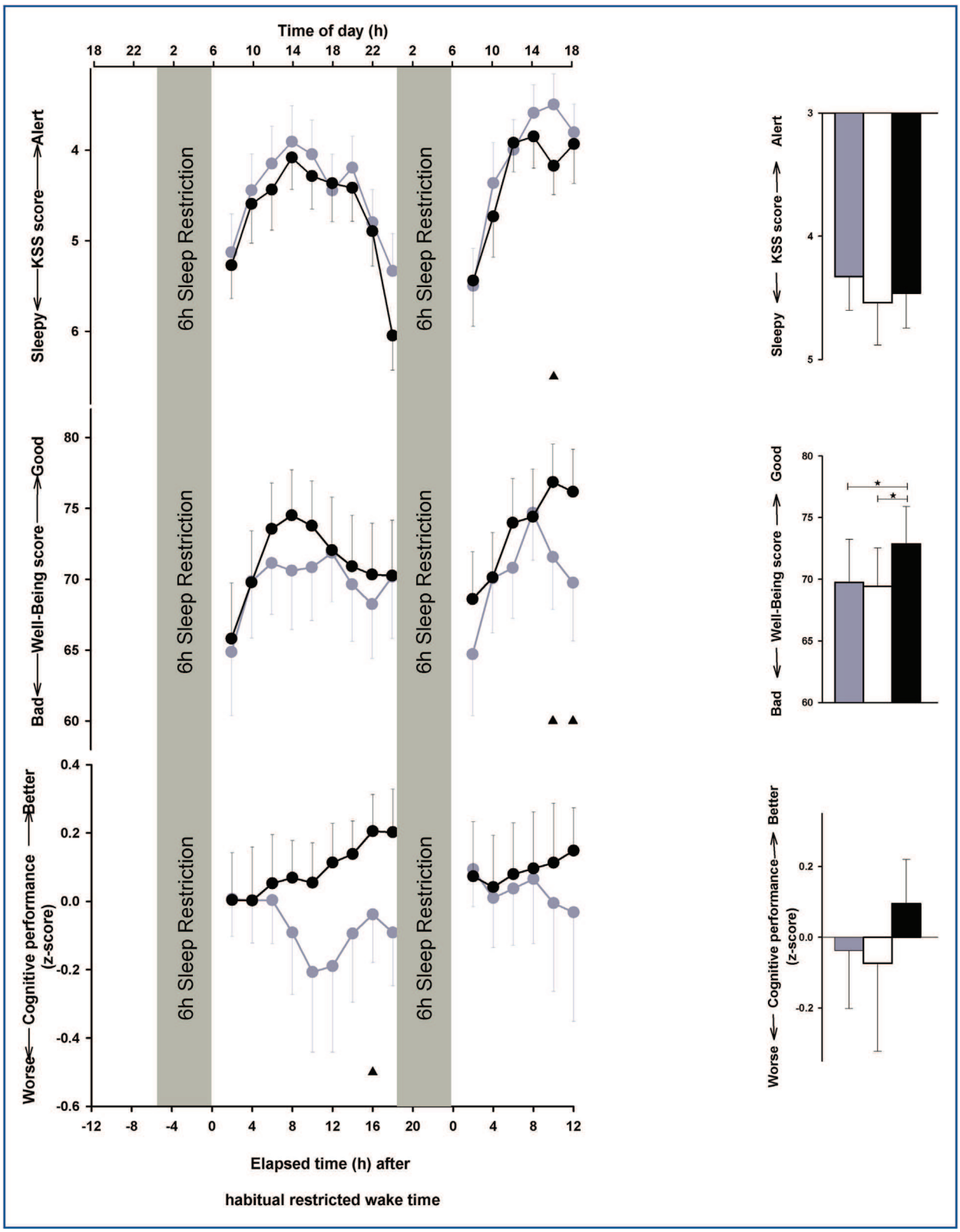

Figure 2. Effet bénéfique du simulateur d'aube. Variation au cours du temps (graphiques de gauche) et moyenne générale (graphique de droite) de (de haut en bas) la fatigue, du bien-être et d'une moyenne des performances cognitives après un réveil *On/Off* (courbe grise) et un réveil simulateur d'aube (courbe noire) chez 17 jeunes hommes soumis à 2 nuits de restriction de sommeil de 6 h. Sur les graphiques de droite, les barres blanches représentent les résultats de conditions témoins : stimulation avec une lumière bleue monochromatique LED 2 heures après le lever. (▲, $p < 0{,}05$).
Figure et légende modifiées de Gabel et al., 2013 [29].

Sur le rythme cardiaque

Il est connu que la transition matinale sommeil-veille provoque une activation maximale du système sympathique, entraînant une augmentation de la vulnérabilité cardiaque après le réveil [37,38]. Ces modulations de la régulation cardiovasculaire, qui résultent de changements brusques dans le contrôle du système nerveux autonome [39], sont d'une importance majeure dans les maladies ischémiques telles que l'infarctus cérébral et du myocarde, l'angine de poitrine, etc [40]. De plus, il a été démontré qu'un dysfonctionnement de l'horloge circadienne était un facteur de risque cardiovasculaire. Les stratégies permettant l'optimisation des rythmes biologiques internes régissant les événements cardiovasculaires peuvent donc être un bon moyen de neutraliser les effets indésirables d'un réveil brusque.

Nous avons récemment découvert, au sein de notre laboratoire, que le simulateur d'aube pouvait constituer l'une de ces stratégies, qui plus est non invasive. En effet, l'accélération rapide du rythme cardiaque lors du réveil est diminuée avec l'utilisation de ce simulateur. Ce réveil en douceur pourrait protéger le cœur par le biais d'une « préparation cardiaque » au processus de réveil, impliquant une préstimulation de l'activité cardiaque 30 minutes avant le réveil. De plus, ces effets de la lumière sur le contrôle cardiaque ne dépendent pas des changements de la structure du sommeil dans la dernière partie de la nuit [41]. Ainsi, le simulateur d'aube joue un rôle protecteur pour les événements de stress cardiovasculaire, qui sont l'une des principales raisons de la vulnérabilité cardiaque accrue après le réveil [37,42].

Maladie

Il est connu depuis quelques temps déjà que la luminothérapie a des effets bénéfiques chez les personnes atteintes de dépression saisonnière, de trouble affectif ou d'hypersomnie. Une telle exposition à la lumière est même plus efficace le matin que le soir.

Ainsi, l'utilisation d'un réveil simulateur d'aube augmente les capacités de réveil chez les patients déprimés et diminue leur fatigue. Plus spécifiquement, on sait que le rythme circadien des patients atteints de dépression saisonnière est décalé de quelques heures, avec un minimum de température vers 5 heures du matin pour un lever à 6 heures, alors que ce minimum se situe à 3 heures du matin chez les sujets sains. Le simulateur d'aube permettrait d'avancer la phase des patients déprimés afin de resynchroniser leur rythme et de diminuer leur fatigue lors du lever [30].

Les luminothérapies utilisant une lumière simulatrice d'aube ou de crépuscule permettent également d'améliorer la qualité du sommeil et d'avancer le moment du coucher chez les personnes âgées atteintes de démence [43].

Limite

Même si le réveil simulateur d'aube peut être utilisé pour diminuer les effets délétères provoqués par la fatigue, lorsque l'organisme est soumis à de fortes pressions de sommeil, comme une restriction répétée de sommeil pendant les jours de travail par exemple, ses effets bénéfiques s'atténuent rapidement. Dès le deuxième jour de restriction, la pression de sommeil devient trop importante pour être contrecarrée par une simple exposition à la lumière.

De plus, étant donné que les effets d'une exposition lumineuse progressive n'ont pas été testés après le réveil, il est difficile d'affirmer que les effets du simulateur d'aube soient attribués au processus de réveil progressif lui-même plutôt qu'à l'exposition lumineuse progressive.

Conclusion

En conclusion, le simulateur d'aube peut être utilisé de façon ponctuelle après une privation ou restriction de sommeil afin d'augmenter les capacités cognitives lors de la journée qui suit ou tout simplement d'améliorer la fatigue, l'humeur et le bien-être avant une bonne nuit de sommeil nécessaire à la récupération. Pour les personnes cherchant à resynchroniser leur rythme interne au rythme environnemental (par exemple, lors de voyages entraînant un changement de fuseau horaire), nous recommanderions plutôt un pulse de lumière monochromatique bleue le matin ou le soir afin d'avancer ou de retarder respectivement le rythme circadien.

Déclaration d'intérêts

Les auteurs déclarent ne pas avoir de conflits d'intérêts en relation avec cet article.

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