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Blue light spectrum and its effects on selected aspects of human sleep and cognition

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Declaration

I declare that the work submitted here is my own and that it has been conducted under the supervision of PhDr. Jana Kopřivová, Ph.D. I also declare that all the used resources have been listed in the References section. No part of this dissertation has been submitted for any other degree.

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Summary

Background: Since the discovery of ipRGCs (intrinsic photosensitive retinal ganglion cells) in the retina, new research possibilities for studying the effects of light on the regulation of various behavioral and physiological functions that are independent of image formation arose. As ipRGCs are most sensitive to light of short wavelengths (460-480nm), this dissertation focuses on current topics related to the use of blue light, emphasizing its influence on circadian rhythms, sleep and cognitive performance and possible applications in clinical and non-clinical settings.
Aims: The first study aimed to explore the effects of 20 minutes of narrow-bandwidth light exposure of different wavelengths on various neuropsychological and neurophysiological parameters of vigilance in healthy volunteers. The objective of the second study was to assess the effect of combining CBT-I (cognitive-behavioral therapy for insomnia) with wearing blue-light blocking glasses 90 minutes before bedtime on subjective and objective sleep parameters and daily symptoms (anxiety, depression, hyperarousal). The third study aimed to examine subjective sleep quality in a population of healthy volunteers and its association with evening and night light exposure to screens of media devices.
Methods: In the first study, twelve healthy volunteers went through 3 sessions of 20 minutes of light exposure of different wavelengths (455, 508, and 629 nm, with an irradiance of 14 μW/cm2), while EEG was recorded (including ERP (event-related potential) P300 and spectral characteristics) and behavioral data (subjective sleepiness, reaction time) gathered. In the second study, 30 patients completed a CBT-I group therapy program, with groups randomly assigned to either active (blue-light filtering glasses) condition, or placebo (glasses without filtering properties) condition. Patients were continually monitored by wristwatch actigraphy, kept their sleep diaries, and completed a standard questionnaire battery at admission and after the end of the program. Lastly, 693 participants in total completed an online questionnaire battery consisting of several sleep-related questionnaires: PSQI, FSS, MCTQ, MEQ and added questions assessing the timing and character of the evening and night exposure to electronic devices (TV, PC, tablets and phones) and the use of various filters blocking short-wavelength light.
Results: Our analyses showed that the short-wavelength light condition (455nm) in the first study, was found to be the most effective in terms of its alerting effect for the following variables: subjective sleepiness, the latency of P300 response and absolute EEG power in higher beta (24-34 Hz) and gamma (35-50 Hz) range. The second study showed a greater reduction of anxiety symptoms in the active vs. placebo group of patients and significant prolongation of subjective total sleep time in the active group. When pre- and post-treatment results were compared in both groups separately, significant differences were observed for the scores in the depression and hyperarousal scales in the active group only. In the active group, there was also a significant reduction of subjective sleep latency and an increase of subjective total sleep time without a change in objective sleep duration, which was significantly shortened in the placebo group. In the third study, our analyses showed that longer cumulative exposure to screen light in the evening was associated with greater sleep inertia in the morning and longer sleep latency on workdays. Furthermore, exposure to screen light 1.5h before sleep or during night awakenings was also associated with a decreased chance to wake up before the alarm time, larger social jet-lag, more pronounce daytime dysfunction, decreased subjective sleep quality, and more fatigue. A statistical trend for an increase in the duration of sleep on weekdays was also found in participants using blue-light filters in the evening hours.
Conclusion: Our results provide valuable insight into the alerting effects of short-wavelength (blue) light. We also show that avoiding blue light in the evening may help reduce the phase-delaying effect of light and facilitate an improvement in sleep parameters and psychiatric symptoms. Altogether, these results may contribute to the development of new lighting or light-filtering systems and may also be applicable for healthy sleep promotion in both the general and clinical populations.

Summary in Czech

Úvod: Od objevu ipRGC buněk sítnice se rozšířily možnosti vědeckého zkoumání vlivu světla na regulaci širokého spektra behaviorálních a fyziologických funkcí nezávislých na tvorbě obrazu. Vzhledem k tomu, že jsou ipRGC nejvíce citlivé na světlo krátkých vlnových délek (460-480nm) se tato dizertace zaměří primárně na vliv modrého světla na cirkadiánní systém, spánek, kognitivní funkce, a možné využití v klinické i neklinické oblasti.
Cíle: Cílem první studie bylo prozkoumat vliv 20-minutové expozice monochromatickému světlu různých vlnových délek na vybrané neuropsychologické a neurofyziologické parametry vigility u zdravých dobrovolníků. Druhá studie zkoumala efekt kombinace KBT-I a večerního nošení brýlí blokujících modré světlo na subjektivní a objektivní parametry spánku a denní symptomy (úzkost, deprese, hyperarousal). Cílem třetí studie bylo prozkoumat subjektivní kvalitu spánku u zdravé populace a její spojitost s večerním a nočním vystavováním se umělému světlu z obrazovek elektronických zařízení.
Metodika: V první studii bylo 12 zdravých dobrovolníků vystaveno celkem třem 20-minutovým expozicím světlu různých vlnových délek (455, 508, and 629 nm, zářivost 14 μW/cm2), při nichž podstoupili měření EEG (vč. EP P300 a spektrálních charakteristik) a behaviorálních proměnných (subjektivní ospalost a reakční čas). Ve druhé studii celkem 30 jedinců s nespavostí absolvovalo standardní psychoterapeutický program pro léčbu nespavosti. Současně byli nahodile přirazeni do aktivní (nosili brýle blokující modré světlo) nebo placebo skupiny (brýle bez filtračních charakteristik), a instruováni k nošení brýlí 90 minut před spánkem. Po celou dobu studie jim byla aktigrafy monitorována pohybová aktivita, denně vyplňovali spánkové deníky a baterii standardních dotazníků administrovaných při přijetí a po ukončení docházky do skupiny. V třetí studii celkem 693 pacientů vyplnilo online baterii dotazníků vztahujících se k spánku (PSQI, FSS, MCTQ, MEQ) a zodpovědělo otázky mapující délku a charakter večerního/nočního vystavení se displejům elektronických zařízení a použití filtrů blokujících modré světlo.
Výsledky: Analýzy v první studii ukázaly, že modré světlo (455nm) mělo nejvýraznější nabuzující účinek, který se projevil v následujících proměnných: subjektivní ospalost, latence P300 odpovědi a absolutní EEG výkon v pásmech vyšší bety (24-34 Hz) a gamy (35-50 Hz). Druhá studie ukázala vyšší pokles symptomů úzkosti v aktivní skupině ve srovnání s placebo skupinou. Současně došlo k signifikantnímu prodloužení subjektivní délky spánku u skupiny s brýlemi filtrujícími modré světlo. Při dalším srovnání efektu intervencí se prokázalo, že v skupině pacientů s brýlemi blokujícími modré světlo došlo k signifikantnímu poklesu skóru v škálach deprese a hyperarousalu, a to pouze u aktivní skupiny. V aktivní skupině se také prokázala signifikantně kratší spánková latence a prodloužení subjektivní délky spánku beze změn v objektivní délce spánku, která se naopak u placebo skupiny zkrátila. V třetí studii bylo zjištěno, že delší kumulativní expozice světlu obrazovek ve večerních hodinách je spojena se silnější spánkovou opilostí následující den ráno a delší spánkovou latencí v pracovních dnech. Dále jsme zjistili, že expozice světlu min. 90 minut před usnutím je spojena s nižší šancí se probudit před budíkem, větším sociálním jet-lagem, výraznějšími denními dysfunkcemi, sníženou subjektivní kvalitou spánku a vyšší únavou. Také se prokázala tendence k delšímu spánku v pracovní dny při používání filtrů blokujících modrou složku barevného spektra.
Závěr: Naše výsledky přinášejí cenný vhled do problematiky modrého světla a jeho prokognitivního účinku. Rovněž přinášejí důkazy o tom, že blokování modrého světla ve večerních hodinách může zmírnit fázový posun, zlepšit kvalitu spánku a přinést úlevu od psychiatrických symptomů. Celkově můžou být tyto výsledky přínosem při vývoji nových systémů osvětlení nebo filtrování světla a mohou mít také preventivní a terapeutický potenciál v obecné i klinické populaci.

Abbreviations

ALAN – artificial light at night
AMA – American medical association
ADHD – attention-deficit hyperactivity disorder
ANS – autonomic nervous system
ANSI – American National Standards Insitute
AUC – area under the curve
BAI – Beck Anxiety Inventory
BB – blue-blocking
BDI – Beck Depression Inventory
Bmal – Brain And Muscle ARNT-Like
BST – bed nucleus of the stria terminalis
CFL – compact fluorescent lamp
CBT-I – cognitive-behavioral therapy for insomnia
CNS – central nervous system
CNV – contingent negative variation
Clock – Circadian Locomotor Output Cycles Kaput
CS – circadian stimulus
CSA – Canadian Standards Association
DLMO – dim light melatonin onset
DLPFC – dorsolateral prefrontal cortex
DMH – dorsomedial nucleus of the hypothalamus
DR – dorsal raphe
DSPD – delayed sleep phase disorder
EEG – electroencephalography
eLORETA – exact low-resolution electromagnetic tomography
EOG – electrooculogram
ERP – event-related potential
ESS – Epworth Sleepiness Scale
EWN – Edinger-Westphal nucleus
fMRI – functional magnetic resonance imaging
FSS – Fatigue severity scale
GLM – general linear model
GHT – geniculo-hypothalamic tract
HAS – Hyperarousal Scale
HC – hippocampus
HD-EEG – high-density electroencephalography
HRV – heart rate variability
ICA – independent component analysis
IGL – intergeniculate leaflet
ipRGC – intrinsic photosensitive retinal ganglion cells
IPS – intraparietal sulcus
ISI – Insomnia Severity Index
KSS – Karolinska Sleepiness Scale
LAN – light at night
LC – locus coeruleus
LED – light-emitting diode
LH – lateral hypothalamus
LHb – lateral habenula
LGN – lateral geniculate nucleus

LPFC – lateral prefrontal cortex
MCH – melanin-concentrating hormone
MCTQ – The Munich ChronoType Questionnaire
MEQ – Morningness-Eveningness Questionnaire
NIF – non-image-forming functions
NMDA – N-methyl-D-aspartate
OPN – olivary pretectal nucleus
Opn4 – opsin 4
ORX – orexin
PAG – periaqueductal grey
Per – Period
PET – positron emission tomography
PLR – pupillary light reflex
pSON – supraoptic nucleus
PSQI – The Pittsburgh Sleep Quality Index
PVN – paraventricular nucleus
PVT – The psychomotor vigilance task
Pul-LP – lateral posterior pulvinar complex
RCT – randomized controlled trial
REM – rapid eye movement
RGB – red-green-blue
RHT – retinohypothalamic tract
RPE – retinal pigment epithelium
Ror – RAR-related orphan receptor
RT – reaction time
SC – superior colliculus
SCA – suprachiasmatic area
SCG – superior cervical ganglion
SCN – suprachiasmatic nucleus
SD – standard deviation
SDS – Sheehan Disability Scale
SEP – somatosensory evoked potential
SPVZ – subparaventricular zone
SWA – slow-wave activity
SWS – slow-wave sleep
TLI – tailored lighting intervention
TST – total sleep time
V1 – visual occipital area
VLPFC – ventrolateral prefrontal cortex
VLPO – ventrolateral preoptic nucleus
VTA – ventral tegmental area
YMRS – The Young Mania Rating Scale

Introduction

The mechanism by which the circadian system perceives light is one of the most exciting discoveries in modern biology. In addition to rods and cones, a third type of photoreceptive cells in the retina, the ipRGC (intrinsically photosensitive retinal ganglion cells), was discovered (Brainard, Hanifin, Rollag, et al., 2001; Hattar, Liao, Takao, Berson, & Yau, 2002; Thapan, Arendt, & Skene, 2001) and opened new research possibilities for studying the effects of light on the regulation of various behavioral and physiological functions that are independent of image formation (termed non-image-forming – NIF visual functions) (LeGates, Fernandez, & Hattar, 2014). The ipRGCs express the photopigment melanopsin and are predominantly sensitive to short-wavelength (blue) light (between 460-480nm).

Initially, the ipRGCs were thought only to influence circadian rhythms, as they integrate and transmit photic information directly to the suprachiasmatic nucleus (SCN), the central circadian pacemaker/oscillator. SCN entrains the circadian timing system to the daily 24-h light/dark cycle and regulates the neural network of melatonin suppression (Blume, Garbazza, & Spitschan, 2019). However, many brain areas other than the SCN also receive direct projections from the ipRGCs and therefore represent vital targets of the NIF system by potentiating effects of light on pupillary constriction, sleep-wake cycle, alertness, and mood (Fernandez et al., 2018; Prayag, Münch, Aeschbach, Chellappa, & Gronfier, 2019). All these functions are not only regulated by natural daylight but are influenced by artificial lighting systems as well. In particular, this is the case in the evening and night hours, as the increasing use of light-emitting devices that contain a considerable proportion of shorter wavelengths of light has been associated with a high prevalence of insufficient sleep, affecting a majority of children (Falbe et al., 2015), adolescents (Hale et al., 2018) and adults (Exelmans & Van den Bulck, 2016; Yang, Yang, Mai, Zhou, & Ma, 2018). Aside from adverse effects of night exposure on our sleep and circadian rhythms (problems with sleep initiation and propensity, melatonin suppression, circadian phase delay, less slow-wave sleep) (Cajochen et al., 2011; Chang, Aeschbach, Duffy, & Czeisler, 2015; J. R. Cho, Joo, Koo, & Hong, 2013; van der Lely et al., 2015; Zeitzer, Fisicaro, Ruby, & Heller, 2014), short-wavelength (blue) light has also been associated with improvements in cognitive functioning (enhancing attention, working and declarative memory as well as executive functions (Cajochen et al., 2011; Gaggioni, Maquet, Schmidt, Dijk, & Vandewalle, 2014; Rahman et al., 2014; Rodriguez-Morilla, Madrid, Molina, & Correa, 2017; Slama, Deliens, Schmitz, Peigneux, & Leproult, 2015; Vandewalle, Maquet, & Dijk, 2009) or decision-making processes (Alkozei, Smith, & Killgore, 2016)).

Thus, applying light or light-filtering interventions and recommendations may lead to new ways of fighting circadian desynchronization and enhancing one's cognitive functioning. Several approaches incorporating blue-light and its filtration will be the main focus of this doctoral thesis.

The thesis is divided into theoretical and research sections. The first chapter of the theoretical summary covers the fundamentals of image- and non-image forming functions of light and light's role in regulating circadian rhythms. It further deals with different aspects and parameters of light and their effect on physiological functions, emphasizing the role of blue (short-wavelength) light that will be the focus of the following chapters. The second chapter aims at exploring the influence of daylight and artificial light on sleep with a focus on melatonin suppression, phase-shift, and changes in sleep micro- and macrostructure. The third chapter explains the possible role of short-wavelength light in cognitive enhancement and underlying physiological mechanisms. The fourth chapter moves on to the chronotherapeutic potential of light and light-blocking interventions. Its main focus is on blocking short-wavelength light, artificial dawn simulation, and possible risks associated with evening and night exposure to artificial light. Finally, the fifth chapter offers some perspectives on future research in this area, emphasizing the use of spectral-tuning or bio-dynamic lighting in creating a circadian-friendly environment for clinical and non-clinical applications and the potential use of metameric light sources.

The experimental part covers three separate studies that are related to the topic of this dissertation. The first study compares light of three different wavelengths (455nm, 508nm, 629nm) and their effect on subjective and objectives parameters of vigilance. Using several electrophysiological and cognitive measures, we aim to provide further evidence regarding the alerting effects of short-wavelength light and thus contributing to future studies and potential applications in lighting or light-filtering technology.

The second study explores the potential of blue-light blocking glasses as an adjunct to a cognitive-behavioral therapy group program in patients with insomnia. This randomized controlled trial aimed to assess the effect of CBT-I (cognitive-behavioral therapy for insomnia) in combination with blue-light blocking glasses intervention that required the patients to wear glasses 90 minutes before scheduled bedtime. Subjective and objective (actigraphy-based) sleep parameters and other related measures (sleepiness, hyperarousal, symptoms of depression, and anxiety) were compared in active and placebo groups, opening new possibilities of using this cheap and easy-to-use chronotherapeutic tool in clinical and non-clinical populations.

The third study, being a large online questionnaire survey, aimed at screening a healthy adult population for the use of screen-based devices during the evening and night hours and its association with subjectively perceived sleep quality and other sleep-related parameters. The main focus of this study was to assess sleep in relation to "light-hygiene" recommendations (avoiding LED screen exposure in the evening and at night). Although the presence of light-hygiene parameters in current literature is very sparse, they are especially crucial for developing future interventions and strategies directly aimed at adhering to sleep (and light) hygiene recommendations with the potential to improve one's sleep.

The final discussion offers insight and concludes the three separate discussions of each of the presented studies, their limitations, and potential perspectives on future research.

LITERATURE OVERVIEW

1 Role of light in the regulation of circadian rhythms

1.1 Image forming and non-image forming visual neural pathways

Specific neural pathways have been described for visual and non-visual systems (Fig. 1). Beginning with the eye, the classical visual (image-forming) system uses mainly rods and cones for image formation but also ipRGCs (intrinsically photosensitive retinal ganglion cells) for rudimentary visual functions. Cones are responsible for photopic vision with high spatial acuity and color discrimination. The photopic system in humans includes three types of cones showing mean peak sensitivity at 555 nanometers (nm), i.e., the green part of the visible light spectrum. S-cones express the short-wavelength-sensitive opsin cyanolabe (420 nm), M-cones express chlorolabe opsin (535 nm), and L-cones express a red-shifted opsin, the erythrolabe (565 nm)(Lucas et al., 2014). Scotopic vision (contrast detection, dim light vision) is sustained by rods using rhodopsin photopigment (λmax 507 nm in humans). Using the optic tract, the pathways of the classical visual system project to subcortical nuclei, such as the thalamic lateral geniculate nucleus (LGN), the lateral posterior pulvinar complex (Pul-LP), and the superior colliculus (SC), before reaching the primary visual area (V1) and then other neocortical regions engaged in dorsal and ventral visual attentional brain pathways (Daneault, Dumont, Masse, Vandewalle, & Carrier, 2016). Animal studies show that ipRGCs also send projections to dorsal LGN (dLGN) and SC. These ipRGC projections play

a role in the conscious perception of spatial brightness and speed motion. Recent evidence also supports the functional role of melanopsin-expressing ipRGC projections to dLGN in visual responses optimization with irradiance detection (Daneault et al., 2016).

However, our eyes are also essential for light-dependent regulation of behavioral and physiological functions that are independent of image formation (termed non-image-forming – NIF visual functions) (LeGates et al., 2014). The ipRGCs expressing the photopigment melanopsin *(Opn4)* are predominantly sensitive to short-wavelength light (between 460-480nm) and have been initially shown to respond to light intrinsically in the absence of rod and cone input. In addition to their intrinsic photosensitivity, all ipRGCs exhibit rod- and cone-mediated, predominantly depolarizing light responses (Schroeder et al., 2018). Nevertheless, melanopsin is the principal photic contributor to most, if not all, non-visual responses (Prayag, Najjar, & Gronfier, 2019). A recent study (Patterson, Kuchenbecker, Anderson, Neitz, & Neitz, 2020) also revealed a novel inhibitory interneuron, an amacrine cell, receiving excitatory glutamatergic input exclusively from S-ON bipolar cells. This S-cone amacrine cell makes highly selective inhibitory synapses onto the ipRGCs, resulting in a blue-OFF response. Accordingly, the S-cone amacrine cell may be a part of an evolutionarily ancient color vision circuit, not for hue perception, but non-image-forming vision. Initially, the ipRGCs were thought to constitute a uniform population whose central role is to influence circadian rhythms. They integrate and transmit photic information via a monosynaptic pathway, the retinohypothalamic tract (RHT) directly to the anterior hypothalamus, to the suprachiasmatic nucleus (SCN), the central circadian pacemaker/oscillator, thereby entraining the circadian system to the daily 24-h light/dark cycle. Signal transduction occurs via the influx of calcium after an interaction with the NMDA receptors to activate the IP3 and ryanodine receptors (Bhadra, Thakkar, Das, & Pal Bhadra, 2017). The ipRGC's contribution to NIF responses to light has also been shown in individuals lacking rod/cone photoreceptors (Vandewalle et al., 2013).

Further investigations in rodents have revealed the existence of at least five subtypes of ipRGCs with different morphological and electrophysiological properties. Together they constitute 4-5% of the total number of RGCs (T. M. Schmidt, Chen, & Hattar, 2011). Their central projections differ amply, reflecting the multiform nature of the non-image-forming visual functions they participate in (Hannibal, Christiansen, Heegaard, Fahrenkrug, & Kiilgaard, 2017).

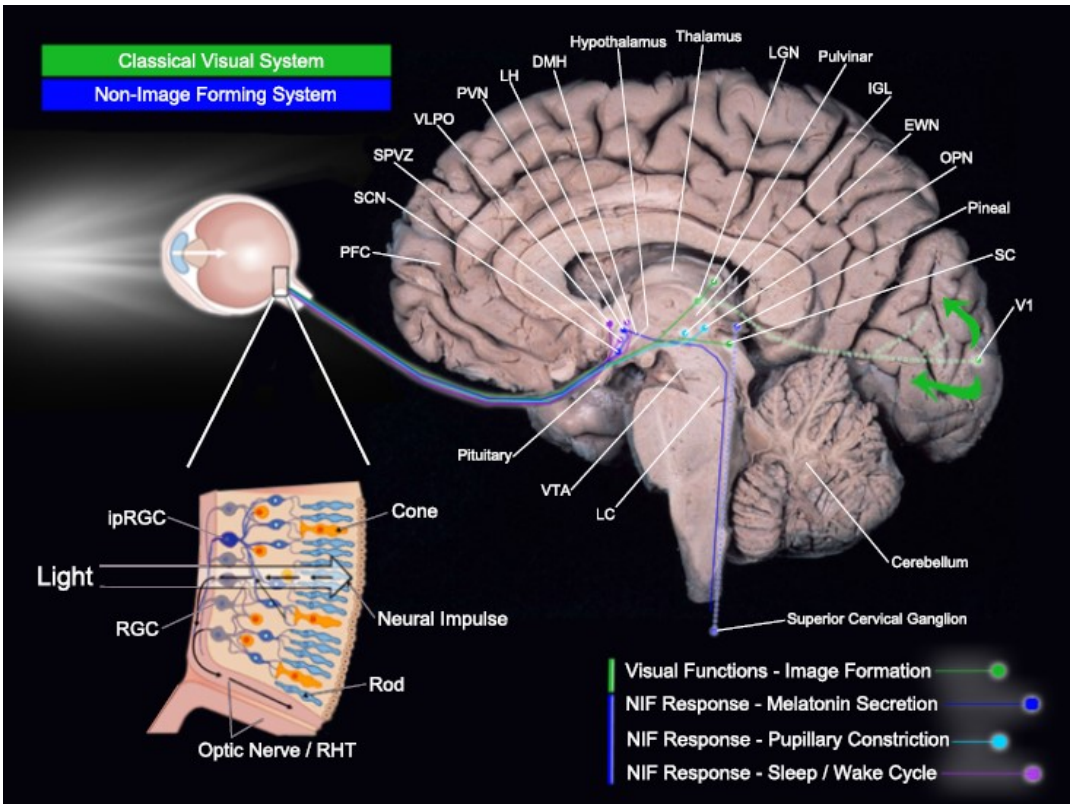

Fig 1. Light-sensitive brain pathways. Simplified brain networks of the classical visual system and the non-image-forming system. Abbreviations: PFC prefrontal cortex, SCN suprachiasmatic nucleus, SPVZ subparaventricular zone, VLPO ventrolateral preoptic nucleus, PVN paraventricular nucleus of the hypothalamus, LH lateral hypothalamus, DMH dorsomedial nucleus of the hypothalamus, LGN lateral geniculate nucleus, IGL intergeniculate leaflet, EWN Edinger-Westphal nucleus, OPN olivary pretectal nucleus, SC superior colliculus, V1 primary visual area, LC locus coeruleus, VTA ventral tegmental area, ipRGC intrinsically photosensitive retinal ganglion cell, RHT retinohypothalamic tract. Adapted from (Daneault et al., 2016).

Moreover, the SCN also indirectly receives light information via another pathway – via the geniculohypothalamic tract (GHT)(Morris, Aeschbach, & Scheer, 2012). Dysfunction of the abovementioned pathways impairs light-induced phase-shifts and entrainment to a light/dark cycle, with a more substantial effect of RHT dysfunction.

The SCN is the endogenous master biological clock responsible for the temporal organization of living organisms by synchronizing internal circadian rhythms and their entrainment with the external environment. SCN sends projections to the hypothalamic and non-hypothalamic structures, including the paraventricular nucleus of the hypothalamus (PVN), the dorsomedial nucleus of the hypothalamus (DMH), and the intergeniculate leaflet (IGL) of the thalamus which also sends projections to the SCN (Daneault et al., 2016). Interactions between the SCN, the superior cervical ganglion (SCG), the PVN, and the pineal gland support the neural network of melatonin suppression. Many brain regions other than the SCN also receive direct projections from the ipRGC. The olivary pretectal nucleus (OPN), the crucial node of the pupillary constriction pathway, receives direct projections

from the ipRGCs. OPN sends projections to the Edinger-Westphal nucleus (EWN), which innervates the sphincter muscle of the pupil allowing pupillary constriction. The ipRGCs also directly project to regions engaged in the regulation of the sleep-wake cycle, such as the ventrolateral preoptic nucleus (VLPO; core region of sleep-wake regulation), the subparaventricular nucleus/zone (SPVZ) of the hypothalamus, involved in sleep regulation but also in motor activity, as well as the lateral hypothalamus (LH), that contains orexin (hypocretin) wakefulness-regulating neurons (Daneault et al., 2016).

Furthermore, light also affects the sleep-wake cycle via the connections between the SCN and the DMH since the DMH also projects to the VLPO, the LH, and the locus coeruleus (LC) (Prayag, Münch, et al., 2019). The amygdala, a structure involved in emotional regulation, also receives direct projections from the ipRGCs and might represent an important target of the NIF system by potentiating effects of light on mood and alertness (described further). The effects of light on the circadian system are well described, although there is new evidence from nocturnal animal studies that ipRGC projections to the SCN can mediate the effects of light on learning, independently from the SCN pacemaker function (Fernandez et al., 2018).

1.2 Light's role in regulating the circadian rhythms

The rotation of the earth about its axis results in periodic changes in the light-dark environment. This predictable change in the light environment enables organisms to confine their activity–rest rhythms and physiological processes to specific times of the day-night cycle. To anticipate changes in the light-dark environment, organisms have evolved an internal biological clock that runs with a period close to 24 hours (LeGates et al., 2014). The master circadian clock (located in the SCN) is a temporal program found in organisms from all phyla. It is an adaptation to earth's rotation, conferring a 24-h structure on processes at all levels - from gene expression to behavior. Circadian clocks are autonomous, producing circa-24-h rhythms even in the absence of daily environmental signals (Roenneberg & Merrow, 2016). The solar day synchronizes circadian rhythms and sleep-wake cycles in animals and limits animals' activity to the correct temporal niche. Under normal conditions, organisms experience a 24-hour light-dark pattern, and the circadian system of most animals uses the day-to-night transitions to align to environmental time.

The circadian clock drives many outputs, which include the sleep-wake and metabolic cycles as well as hormonal changes. Proper alignment between light, the circadian

clock, and output behaviors produces a temporal order in organisms that is essential for survival (Hastings, Reddy, & Maywood, 2003). The circadian system is orchestrated by a master clock, located in the SCN of the hypothalamus, and entrained to the 24-h light-dark cycle via exposure to light. The master clock synchronizes peripheral clocks located in other tissues outside the SCN, e.g., in the liver, lung, muscle, retina, kidney, or cortex (Buijs et al., 2006). Although the molecular machinery (transcription-translation feedback loops) that drives circadian rhythms in SCN and peripheral cells is similar (Yagita, Tamanini, van Der Horst, & Okamura, 2001), the synchrony between peripheral clocks within organs is lost without input from the SCN.

The core genes of the mammalian circadian clock comprise 14 genes, including members of the Per, Cry, Bmal, Clock, Ror, and Rev-Erb families, that show an interaction via the positive and negative feedback loops of the transcription and translation (Fig. 2). The circadian day ensues with the CLOCK/BMAL1 activator heteromeric complex formation, which binds the E-box sequences at the promoter of the genes, Per, Cry, Ror, and Rev-Erb. The two major loops, REV-ERB/Bmal/ROR and PER/CRY loops interconnect. The transcription of the Per 1, 2, 3, and Cry 1, 2 genes activates in the PER/CRY loop and, in turn, inhibits the transcription of the clock genes via the CLOCK/BMAL1. The REV-ERB/Bmal/ROR loop helps in driving the self-sustained oscillations. Both of the loops operate independently but need to interconnect concomitantly to produce oscillations within a period of 24 h (Lowrey & Takahashi, 2011; Relogio et al., 2011).

Light is the most potent "time giver" (German: *zeitgeber*), or time cue, to the master circadian oscillator. The effect of light upon the circadian system is dependent on the internal time of exposure (the circadian time or, more precisely, the time predicted by the circadian period). Light exposure during the biological evening/early night (i.e., a time generally associated with the start of behavioral inactivity in diurnal animals and behavioral activity in nocturnal species) phase delays the circadian rhythm (i.e., causes the circadian cycle to shift later relative to clock time or, more precisely, relative to that predicted by the circadian period).

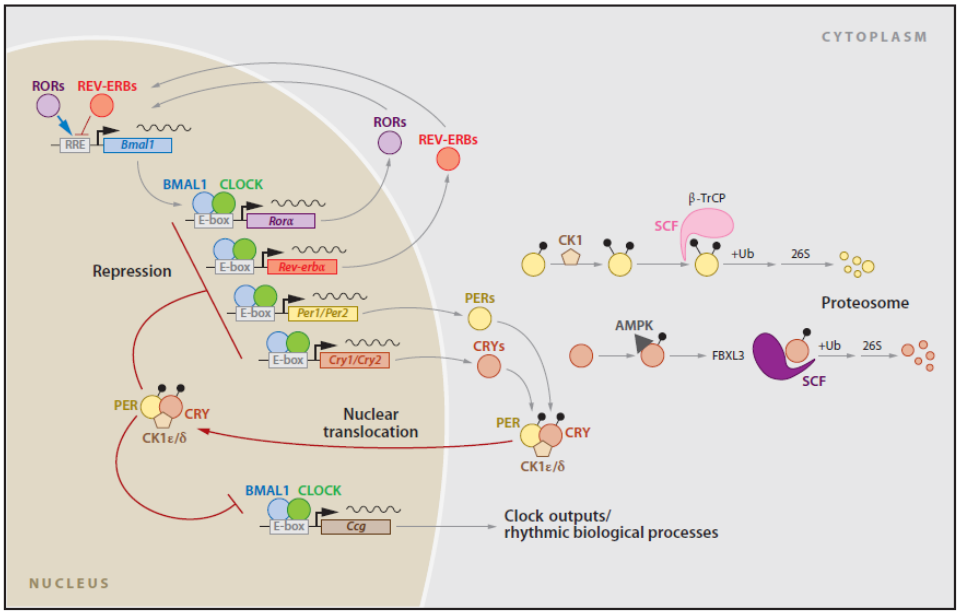

Fig 2. The molecular mechanism of the circadian clock in mammals. Constituting the core circadian clock is an autoregulatory transcriptional feedback loop involving the activators CLOCK and BMAL1 and their target genes Per1, Per2, Cry1, and Cry2, whose gene products form a negative-feedback repressor complex. In addition to this core transcriptional feedback loop, other feedback loops are also driven by CLOCK:BMAL1. One feedback loop involving Rev-erbα and Rorα that represses Bmal1 transcription leads to an antiphase oscillation in Bmal1 gene expression. CLOCK:BMAL1 also regulates many downstream target genes known as clock-controlled genes(Ccg). At a post-transcriptional level, the stability of the PER and CRY proteins is regulated by SCF (Skp1-Cullin-F-box protein) E3ubiquitin ligase complexes involving β-TrCP and FBXL3, respectively. The kinases, casein kinase 1ε/δ (CK1ε/δ) and AMP kinase(AMPK), phosphorylate the PER and CRY proteins, respectively, to promote polyubiquitination by their respective E3 ubiquitin ligase complexes, which in turn tag the PER and CRY proteins for degradation by the 26S proteasome complex—adapted from (Mohawk, Green, & Takahashi, 2012).

On the other hand, light exposure during the biological morning (i.e., typically the transition from behavioral inactivity to activity in diurnal species; and vice versa in nocturnal animals) results in a phase advance, i.e., causes the circadian cycle to shift earlier relative to clock time (Morris et al., 2012). Responses to light have been further shown to depend on intensity, duration, timing, temporal pattern, the spectral content of the light stimulus, and prior photic history (Prayag, Najjar, et al., 2019).

1.3 Responses to light

1.3.1 Spectral sensitivity to light

The pattern of melatonin secretion, considered as one of the best indirect markers of the circadian clock in the SCN (Arendt, 1998), can be most effectively suppressed by light that peaks at ~480 nm (Brainard, Hanifin, Greeson, et al., 2001; Thapan et al., 2001), which is the same as that of ipRGCs sensitivity (Berson, Dunn, & Takao, 2002)(Fig. 3).

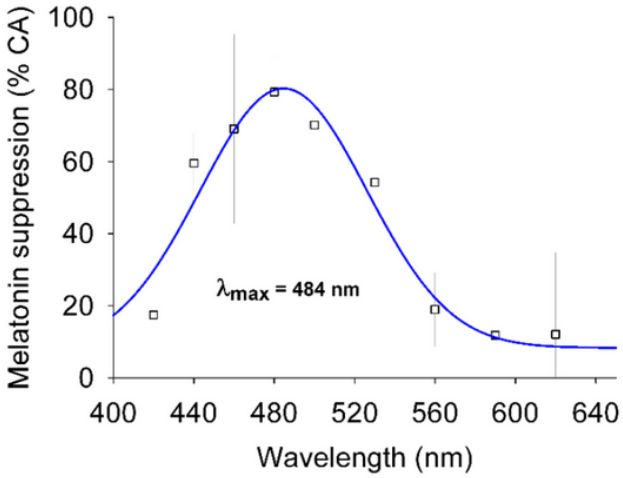

Fig 3. Action spectrum of acute melatonin suppression by light in humans. Wavelength-dependent suppression of melatonin (expressed relative to control-adjusted (CA) suppression of melatonin) after 60 minutes of monochromatic light exposures at night. Adapted from (Najjar, Chiquet, et al., 2014).

Brainard et al. have also shown that polychromatic light is more potent for melatonin regulation when enriched in the short-wavelength spectrum (Brainard et al., 2015). Phase-shifting responses mediated by the master clock are also more sensitive to short-wavelengths of 460–470 nm when compared to medium wavelengths at 555 nm (Lockley, Brainard, & Czeisler, 2003) or long-wavelength light at 600 nm (Revell, Arendt, Terman, & Skene, 2005). At the behavioral level, blue light (460 nm) is more effective in enhancing brain responses than green light (550 nm) in vigilance (Lockley et al., 2006), higher executive (Vandewalle, Schmidt, et al., 2007) and working memory (Vandewalle, Gais, et al., 2007) tasks.

Other studies comparing sources of lighting based on their CCT (Correlated color temperature) show that exposure to sources with higher CCT (and thus more short-wavelength light) (Katsuura & Lee, 2019; Yasukouchi & Ishibashi, 2005) leads to an increase in arousal levels, autonomic nervous system activation (including heart rate variability, blood pressure, and body temperature regulation) and changes in sleep architecture. Wavelength comparisons by Hanifin et al. (Hanifin et al., 2019) have also indicated that circadian phase-shifting and enhancement of subjective and EEG correlates of alertness have a higher sensitivity to short-wavelength visible light. Blue-enriched light (17000K) caused significantly higher suppression of melatonin and significant improvement in alertness than standard light (4000K). These results suggest a primary mediation through melanopsin-based phototransduction (Bourgin & Hubbard, 2016), although Sasseville et al. (Sasseville, Martin, Houle, &

Hebert, 2015) have argued that the improvement in alertness cannot be solely attributed to short-wavelength light through ipRGCs.

1.3.2 Duration of light exposure

Light exposure duration also plays a determinant role. Chang et al. (Chang et al., 2012) studied the impact of a 10000 lux light exposure of different durations on circadian phase-shift and suppression of melatonin. They found that the responses to light were non-linear with respect to exposure duration. Half of the melatonin phase shift was gained with 2.7 h duration and half of the maximum value of melatonin suppression percentage with 1.9 h duration. Dewan et al. (Dewan, Benloucif, Reid, Wolfe, & Zee, 2011) showed that increasing the duration of the light exposure from 1 to 3 hours, but not the intensity (between 2000 to 8000 lux), increased the magnitude of light-induced phase delays. Although the intensities of light used in the latter study were likely saturating the response, the results emphasize that the magnitude of the circadian response depends simultaneously on light exposure duration and intensity. The relationship between the length of light exposure and response is more complex, as sequences of very short light pulses can also induce significant phase shifts in humans (Najjar & Zeitzer, 2016; Zeitzer, Ruby, Fisicaro, & Heller, 2011), with no difference between 15-second or a 2-minute pulse of bright light, as demonstrated in a study (Rahman, St Hilaire, Chang, et al., 2017) where a 9500 lux, 4100K fluorescent light was used (Prayag, Münch, et al., 2019). Another study (Tonetti & Natale, 2019) showed that even a single short (1 min) exposure to blue light is enough to enhance the response to cognitive tasks. Studies by Figueiro et al. (Figueiro, 2015; Figueiro, Bierman, & Rea, 2013) have also shown that 2-second pulses of 480nm light significantly delayed circadian phase (DLMO) and suppressed nocturnal melatonin.

Furthermore, Vandewalle et al. have shown that 20 minutes of bright white light-induced both thalamic and cortical modulations that started to decline swiftly after the end of the exposure but outlasted the exposure by several minutes (Vandewalle et al., 2006). Exposure to monochromatic light of similar duration but composed of 100 times fewer photons modulated activity of similar brain areas, but these responses did not seem to outlast the exposure (Vandewalle, Gais, et al., 2007). Also, when the duration of light exposure was reduced to less than a minute to identify brain areas involved in establishing non-visual responses to light, the effects were mostly restricted to subcortical structures such as the dorso-posterior thalamus and the brainstem (LC-compatible area), and the number of cortical modulations was significantly reduced (Vandewalle, Schmidt, et al., 2007).

1.3.3 Timing of light exposure

Responses to light are also dependent on the timing of exposure (Khalsa, Jewett, Cajochen, & Czeisler, 2003; Ruger et al., 2013; St Hilaire et al., 2012). Time of day effects have also been described for acute responses to light, such as changes in heart rate and temperature. Nighttime exposure significantly increased those responses, whereas exposures during the daytime period did not (Ruger, Gordijn, Beersma, de Vries, & Daan, 2006). With 6.7 h polychromatic light exposure at 10000 lux, a maximum phase delay of 3.6 h, and phase advance of 2.01 h was obtained by Khalsa et al. (Khalsa et al., 2003). With 6.5 h of monochromatic light exposure at 480 nm, almost the same curve was observed at much lower illuminance levels, suggesting that shorter-wavelength light of 480 nm is accounting almost entirely for light-resetting of the circadian clock (Ruger et al., 2013).

1.3.4 Light intensity

Light-dependent circadian responses are also sensitive to the intensity of the exposure (Cajochen, Zeitzer, Czeisler, & Dijk, 2000; Prayag, Najjar, et al., 2019; Zeitzer, Dijk, Kronauer, Brown, & Czeisler, 2000), which is in studies usually expressed by illuminance, luminance, irradiance, etc. Zeitzer and colleagues (Zeitzer et al., 2000) found that melatonin phase shift response saturated at about 550 lux, with no measurable response detected below 15 lux, consistent with the results by Boivin and colleagues (Boivin, Duffy, Kronauer, & Czeisler, 1996). For the suppression of melatonin, saturation was found at about 200 lux, with no measurable response to light below 30 lux. Suppression of melatonin in response to 18 different office light conditions (30-minute exposure) revealed a dose-response relationship, that was best predicted by the melanopic lux of the lighting (a unit for the melanopic spectral efficiency function, an indicator for the biological impact of different lighting conditions) (Nowozin et al., 2017). More recent results by Prayag et al. (Prayag, Najjar, et al., 2019), show much lower thresholds, with a response at 1.5 melanopic lux (which corresponds to 1.5–9 photopic lux) and saturation at 305 melanopic lux. Aside from nocturnal melatonin suppression, a smaller number of papers have also addressed the influences of light intensity of short exposure on the central nervous system (CNS) (Higuchi, Watanuki, Yasukouchi, & Sato, 1997; Noguchi, Sakaguchi, & Sato, 1999; Yoshinaga, Fujita, Tanaka, & Nemoto, 2011), the ANS as assessed by measurements such as HRV (Noguchi et al., 1999), body temperature regulation (Kakitsuba, Mekjavic, & Katsuura, 2011), and serum tryptophan concentration and visuomotor and sensorimotor performance (Schobersberger et al., 2018).

1.3.5 Temporal patterns

Rimmer et al. (Rimmer et al., 2000) and Gronfier et al. (Gronfier, Wright, Kronauer, Jewett, & Czeisler, 2004) showed that intermittent bright light pulses produced a similar response of the phase shift and suppression of melatonin in humans. Six 15-minute pulses of 9500 lux polychromatic white light separated by 60 minutes of dim light produced a similar phase shift as a continuous 6.5 h exposure at 9500 lux (with just 1/4 of the light exposure in duration). Light pulses (45 min light exposures, separated by 60 min of 100 lux) have also been shown to efficiently delay the phase and entrain the circadian system to longer-than-24 h period (Gronfier, Wright, Kronauer, & Czeisler, 2007). Strikingly, Zeitzer et al. (Zeitzer et al., 2011) obtained a phase delay of 45 minutes by using sixty 2-ms pulses (corresponding to 120 ms total duration) of 473 lux of white light. For 2 ms light pulses of 1700–1800 lux, an optimal interstimulus interval, that elicited the maximum phase-delay response during the night, was determined to be 7.6s (Najjar & Zeitzer, 2016). Revell et al. (Revell, Molina, & Eastman, 2012), using three periods of 30-min blue-light exposure separated by 15-min intervals, obtained average phase shifts of about 1 h. These results confirm that the light exposure pattern, even with very short pulses, can strongly influence light-dependent acute and circadian physiology. Vandewalle et al. (Vandewalle, Schmidt, et al., 2007) have shown that blue, short-wavelength light increased brain activity within the very first seconds of the exposure suggesting a prominent contribution of melanopsin-expressing retinal ganglion cells to brain responses to light at the exposure onset.

1.3.6 Prior light history

Prior light history has been shown to influence the sensitivity of ipRGCs that mediate NIF photoreception (Wong, Dunn, & Berson, 2005). These neurons show light and dark adaptation; they can become ‘desensitized’ after exposure to a brief flash of light and ‘resensitized’ after time in darkness. Human studies show that prior light exposure impacts melatonin suppression (Hebert, Martin, Lee, & Eastman, 2002; Jasser, Hanifin, Rollag, & Brainard, 2006; Smith, Schoen, & Czeisler, 2004). For example, prior exposure to a week of daytime low-intensity light stimulus (<200 lux) significantly increased melatonin suppression, as compared to nighttime polychromatic light exposure (5000–7000 lux) (Hebert et al., 2002). Nighttime light exposure also showed no decrements of melatonin concentration after day-time exposure to 900 and 2700 lux bright light as compared to lower day-time light intensities (<10, 100, and 300lx) in a study by Kozaki et al. (Kozaki, Kubokawa, Taketomi, & Hatae, 2015). Furthermore, dim white light adaptation attenuated melatonin suppression

by subsequent exposure to monochromatic light of shorter wavelengths as compared to dark adaptation (Jasser et al., 2006). Similarly, when individuals were exposed to two different lights (very dim light vs. typical room light) before 6.5 h light exposure at night, the prior exposure to very dim light level, as compared to standard room light level, caused a more significant melatonin rhythm phase shift and acute melatonin suppression (Chang, Scheer, & Czeisler, 2011). The effects of prior light exposure also impact cognitive brain functions, with prior exposure to longer wavelength (~589 nm) as compared to shorter-wavelength light (~461 nm), resulting in increased activation in brain regions associated with executive control (Chellappa et al., 2014). Furthermore, prior illuminance history has also been shown to influence the magnitude of the direct alerting effect of a light stimulus (Chang, Scheer, Czeisler, & Aeschbach, 2013). Importantly, recent findings show that prior light exposure can also reduce the subsequent responsivity of the inner clock, such that bright blue-enriched polychromatic morning light exposure, as compared to a control lighting, reduced phase shifts in response to evening light exposures (Munch et al., 2016). Also, it is essential to mention the ability of the non-visual light system of healthy young subjects to adapt to changes in the spectral composition of environmental light exposure, as found by a study by Gimenez et al. (Gimenez, Beersma, Bollen, van der Linden, & Gordijn, 2014).

1.3.7 Spatial distribution

Acute and circadian effects of different spatial stimulation of the retina have been shown in humans (Prayag, Münch, et al., 2019). Salivary melatonin suppression by light is more effective when the nasal retina is exposed compared to the temporal retina (Visser, Beersma, & Daan, 1999). Glickman et al. (Glickman et al., 2003) found that exposing the superior area of the retina was less effective in suppressing melatonin compared to the inferior retina. Rüger et al. (Ruger, Gordijn, Beersma, de Vries, & Daan, 2005) investigated the influence of the stimulation of retinal area in the NIF responses of melatonin suppression, phase delay, subjective sleepiness, and core body temperature. They found that nasal illumination of the retina resulted in more robust melatonin suppression and circadian phase delay compared to temporal illumination. Recent characterization of the distribution and subtypes of the ipRGCs in the human retina (Hannibal et al., 2017) suggest diverse ipRGCs functionalities. Also, in rodents, different ipRGCs subtypes have been associated with different functions (for review (T. M. Schmidt et al., 2011)). Stimulating the retina in an eccentricity-dependent manner, at constant irradiance, resulted in an increasing post-illumination pupil response amplitude (Joyce, Feigl, & Zele, 2016) in humans. These results suggest that the

percentage of classical photoreceptors and ipRGCs subtypes stimulated in the retina can play a role in the magnitude of acute responses to light (Prayag, Münch, et al., 2019).

1.4 Light measurement recommendations

To measure and compare the biological effects of light, Prayag et al. (Prayag, Münch, et al., 2019) recommend using absolute metrics (irradiance, photon flux), measured on a vertical plane at the eye level, as they are absolute measures not weighted to the sensitivity of the human photopic luminosity function (as lux is). Another recently proposed metric ('melanopic lux') (Lucas et al., 2014) also allows integration of spectral characteristics and intensity of any light source, accounts for lens transmission, and is an estimate of the effective illuminance perceived by ipRGCs.

Recently, a new international standard (CIE S 026/E:2018(l'Eclairage, 2018)) recommended using melanopic irradiance as the best and most straightforward metric to model human NIF responses in most real-life scenarios. For the melatonin suppression response, Prayag et al. (Prayag, Najjar, et al., 2019) showed that melanopic irradiance could also be used as a simple metric to model the response and account for most of the suppression.

Spitchan et al. (Spitschan, Lazar, & Cajochen, 2019) also argued that when quantifying the optical effects of optical filters, the spectral transmittance, which specifies the amount of light transmitted as a function of wavelength may not be sufficient enough. They proposed a novel (physiologically relevant and retinally referenced) framework for quantifying the visual and non-visual effects of filters, incorporating the luminous transmittance, the melanopsin transmittance, the color shift, and the gamut reduction. They suggest that future studies and examinations of the physiological effects of optical filters should quantify both the visual and non-visual effects of the filters beyond the spectral transmittance, which will eventually aid in developing a mechanistic understanding of how different filters affect physiology. They strongly discourage comparing the downstream effects of different filters on sleep or circadian responses, without considering their effects on the retinal stimulus (Spitschan et al., 2019).

2 Light and its influence on sleep

2.1 Influence of daylight

As mentioned above, light is the key zeitgeber of the circadian system and interacts with the master clock located in the SCN via non-image-forming pathways connecting retina and the SCN. Unsurprisingly, light, therefore, also affects sleep (Blume et al., 2019). The

phase-advancing effects of daylight have been reported by Roenneberg and colleagues (Roenneberg, Wirz-Justice, & Merrow, 2003) who, using questionnaire data, found that each additional hour spent outdoors advanced sleep by approximately 30 minutes. Despite light being the most potent zeitgeber, this phase advance could also result from physical exercise during daytime (Wright et al., 2013; Youngstedt, Elliott, & Kripke, 2019), as it is often confounded with time spent outdoors. Moreover, light exposure during the day has also been shown to affect the duration of sleep. Shorter daylight exposure and longer nights are associated with a longer biological night as indexed by the duration of melatonin secretion, and thus longer sleep duration (Boubekri, Cheung, Reid, Wang, & Zee, 2014; Stothard et al., 2017), which may also reflect a seasonality effect (Yetish et al., 2015).

Beyond this, sleep quality is also affected by light exposure during the day. Several studies report that daytime exposure to light enriched in short-wavelengths was associated with increased fatigue in the evening (Viola, James, Schlangen, & Dijk, 2008), and sleep quality (Boubekri et al., 2014; Figueiro et al., 2017; Viola et al., 2008), decreased sleep-onset latency (Figueiro et al., 2017) and increased slow-wave sleep accumulation (Wams et al., 2017), which may be related to the dissipation of the homeostatic sleep pressure. Wams and colleagues (Wams et al., 2017) also report that participants with later exposure to light had more nocturnal awakenings and less slow-wave sleep. Postulating that optimal light exposure is a predictor for consolidated sleep-wake rhythms and high sleep quality implies that the exposure of light during the day should be sufficiently long and/or bright and/or rich in short-wavelengths at 480 nm (Prayag, Münch, et al., 2019). In agreement with this proposal, increasing the short-wavelength content of light during daytime was found to increase the duration of sleep and to correct circadian phase delay in extreme conditions of chronic artificial light exposure (without daylight) (Najjar, Wolf, et al., 2014). Recent field study data also demonstrated the association of higher light intensity exposure during daytime with more significant slow-wave sleep (SWS) accumulation on the following night as well as shorter sleep latency to stage 2 sleep (Wams et al., 2017).

2.2 Exposure to artificial lighting, smartphones, and visual display units

In addition to natural daylight, humans are also exposed to a considerable amount of artificial light. In particular, this is the case in the evening hours, when the circadian system is most sensitive to light-induced phase delays. Artificial light can, therefore, delay the timing of the circadian clock and thus sleep (Blume et al., 2019). Light from LED screens has repeatedly been suggested to interfere with the physiological processes involved in sleep

(e.g., melatonin secretion (Cajochen et al., 2005)). The widespread use of portable electronic devices and the normalization of media devices in the bedroom is accompanied by a high prevalence of insufficient sleep, affecting a majority of children (Falbe et al., 2015), adolescents (Hale et al., 2018) and adults (Exelmans & Van den Bulck, 2016; Yang et al., 2018). Bright light exposure in the evening has become a problem with the increasing use of light-emitting devices in the evening, especially in adolescents whose internal sleep-wake preferences are already delayed (Touitou, Touitou, & Reinberg, 2016). Most light-emitting devices (LED based) contain a considerable proportion of shorter wavelengths of light, which have potent (adverse) effects on sleep initiation and propensity when exposure occurs before bedtime (Cajochen et al., 2011; Figueiro & Rea, 2016; Figueiro, Wood, Plitnick, & Rea, 2011; Chang et al., 2015; van der Lely et al., 2015). Many studies have also shown the phase delaying effects of different light exposures in the evening on the following sleep episode (Gordijn, Beersma, Korte, & van den Hoofdakker, 1999; Komada, Tanaka, Yamamoto, Shirakawa, & Yamazaki, 2000; Santhi et al., 2012). Even more, since LAN (light at night) is penetrating through closed eyelids (while subjects are asleep), high-intensity LAN can suppress melatonin levels and delay circadian phase (Hatonen, Alila-Johansson, Mustanoja, & Laakso, 1999; Zeitzer et al., 2014), whereas the sleep architecture and the number of sleep-wake transitions are not affected (Zeitzer et al., 2014). Nevertheless, constant bed lights at night were shown to be associated with less slow-wave sleep (SWS) in younger subjects (J. R. Cho et al., 2013) and greater depressive symptoms in a sample of elderly living at home (Obayashi, Saeki, & Kurumatani, 2018).

Evaluating sleep objectively with EEG, Münch and colleagues (Munch et al., 2006) found that exposure to short-wavelength light for two hours starting 3h before bedtime leads to decreased slow-wave activity (SWA) and thus shallower sleep. From this, the authors conclude that the alerting effects of short-wavelength light persist into sleep. This is in line with findings by Chellappa and colleagues (Chellappa et al., 2013), who reported a tendency for less frontal non-rapid eye movement EEG power density (a functional index of homeostatic sleep pressure) after exposure to 6500K light, compared to light at 2500 K and 3000 K. However, short-wavelength light exposure in the evening was also associated with increased SWA later during the night, suggesting a possible compensatory mechanism (Munch et al., 2006). Exposure to short-wavelength light in the evening/night was also shown to elicit acute alerting effects and prolonged sleep latencies (as shown in young adults, e.g. (van der Lely et al., 2015), and young children (Akacem, Wright, & LeBourgeois, 2018)). When using light-emitting devices in the evening participants averaged nearly 10 min longer to fall

asleep than in the print-book condition in a study (Chang et al., 2015) by Chang et al. Participants also had significantly less rapid eye movement (REM), reflecting a lower average rate of accumulation of REM sleep during sleep. Reading the light-emitting e-book was associated with decreased sleepiness in the evening. An hour before bedtime, study participants rated themselves as less sleepy, and their EEG showed less power within the delta/theta frequency range. The following morning, however, the results for self-reported sleepiness were reversed, with participants feeling sleepier the morning after reading a light-emitting e-book the prior evening. Reading from an iPad also decreased subjective sleepiness, delayed the EEG dynamics of slow-wave activity by approximately 30 min, and reduced slow-wave activity after sleep onset compared to reading from a standard paper book (Gronli et al., 2016). Chang and colleagues (Chang et al., 2015) found that reading a book from an e-reader for 4 hours before sleep increased sleep onset latency, delayed the timing of the biological clock, reduced evening sleepiness, melatonin secretion, as well as next-morning alertness, which is also in line with other findings (Santhi et al., 2012; Zeitzer et al., 2014). Rangtell and colleagues (Rangtell et al., 2016) examined the effects of reading a novel on a tablet computer vs. in a physical book as well. Reading for two hours following prolonged (6.5h) exposure to bright light between 2:30 pm and 9 pm, contrasting other findings did not suppress melatonin or alter subjective and objective sleep parameters. Note, though, that exposure was shorter than in studies that reported significant effects (Chang et al., 2015; Santhi et al., 2012; Zeitzer et al., 2000).

Subjective alertness and wake EEG activity in the alpha range (9.75–11.25 Hz) were also higher during light exposure in the evening when compared to the pre-light exposure. The light exposure produced circadian phase shifts and significantly prolonged latency to rapid-eye-movement (REM) sleep. The increase in wake EEG alpha activity during light exposure was negatively correlated with REM sleep duration (Munch et al., 2011).

Several studies have also reported that smartphone ownership and use before bedtime may be associated with more self-reported sleeping problems (Schweizer, Berchtold, Barrense-Dias, Akre, & Suris, 2017), decreased sleep efficiency, longer sleep onset latency and poor sleep quality (Christensen et al., 2016), and delays sleep thereby also shortening sleep duration (Christensen et al., 2016; Lemola, Perkinson-Gloor, Brand, Dewald-Kaufmann, & Grob, 2015; Schweizer et al., 2017).

Evening exposure to long-wavelength light was shown to have sleep-promoting effects by shortening sleep onset and increasing sleep duration in rodents (Pilorz et al., 2016). In humans, depleting the short-wavelength content of ambient light for 8h before bedtime

resulted in increased EEG delta-theta activity and reduced melatonin suppression before bedtime (Rahman, St Hilaire, & Lockley, 2017).

More recently, it was also demonstrated that filtering shorter wavelengths of light (Ostrin, Abbott, & Queener, 2017) or using orange/red light exposure (Munch et al., 2016; van der Meijden et al., 2018) in the evening increased sleep duration (Munch et al., 2016; Ostrin et al., 2017), sleep propensity (van der Meijden et al., 2018), without suppressing melatonin (Munch et al., 2016; Ostrin et al., 2017), as also shown by several human studies including those with novel approaches of spectral tuning (Rahman, St Hilaire, & Lockley, 2017) and metameric light (Allen, Hazelhoff, Martial, Cajochen, & Lucas, 2018). The exact sleep-promoting mechanisms of light of longer wavelengths in the evening still need to be further elucidated. A different mode of action by melanopsin-dependent neuronal projections to the SCN and the VLPO might play a role, as proposed in mice (Cajochen & Chellappa, 2016; Pilorz et al., 2016). Taken together, the different characteristics of light exposure across the day can lead to changes in sleep timing, propensity, architecture, and sleep EEG power spectra.

Aside from spectral characteristics, several mechanisms have been put forward to explain how media use might affect sleep quality. Exposure to light from electronic devices can also alter thermoregulation (mediated via melatonin suppression), and subjective feelings of sleepiness, and mood (Higuchi, Motohashi, Liu, Ahara, & Kaneko, 2003; Sroykham & Wongsawat, 2013). Secondly, evening and night exposure to blue light may enhance alertness or performance by increasing cortical arousal (discussed in the following chapter). Furthermore, excitement and stimulation of media content may also potentiate arousal and therefore result in difficulties falling asleep or poor sleep quality (Gradisar et al., 2013). Another mechanism mentioned by Exelmans and Van den Bulck (Exelmans & Van den Bulck, 2016) is called sleep displacement, which refers to increased time in bed before attempting to go to sleep, and shorter sleep duration as a result of extensive media use in the hours before sleep (Kubiszewski, Fontaine, Rusch, & Hazouard, 2013). Artificial light at night (LAN) may pose a health risk, e.g., for circadian desynchronization, tumor proliferation, depression, or sleep disorders in humans (Hatori et al., 2017) and will be further discussed in the following parts of the thesis.

3 Light and its role in enhancing cognitive functions

3.1 Neural circuitry

The efferent projections of the ipRGCs include multiple hypothalamic, thalamic, striatal, brainstem and limbic structures (Hattar et al., 2006) but the functional significance of most of these projections has not been elucidated (see Fig. 4). The brain areas that may be involved in the non-visual effect of light beyond these ipRGC projections are also unknown. Nevertheless, if we only consider the number of brain areas that are just one synapse away from ipRGCs, and the numerous projections of just one key target of ipRGCs, the suprachiasmatic nucleus (SCN) of the hypothalamus, site of the principal circadian clock (Saper, Lu, Chou, & Gooley, 2005), it becomes evident that non-visual responses to light could affect many brain functions, including cognitive functions.

In addition to SCN activation by light, several hypothalamic regions involved in the modulation of alertness are directly managed through projections from the ipRGCs and/or indirectly controlled by light because of the projections from the SCN (Aston-Jones, 2005; Perrin et al., 2004; Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle, Maquet, et al., 2009). These hypothalamic areas are, for example, the ventral lateral preoptic area (VLPO) and locus coeruleus (LC). The VLPO is well studied for its distinct function in sleep regulation and arousal, which influence the level of alertness (Lok, Smolders, Beersma, & de Kort, 2018).

Another hypothalamic-associated area implied in the regulation of alertness is the LC, a dense cluster of norepinephrine neurons, and a source of efferent projections to multiple CNS regions (Aston-Jones, 2005). In primates and rats, indirect projections have been identified from the SCN to the LC via the dorsomedial hypothalamic nucleus. Direct effects of light have also been found in humans, where light modulates brain activity in an area compatible with LC neurons. Both the LC and dorsal raphe (DR) have been indicated to play an essential role in wakefulness promotion (Mieda & Yanagisawa, 2002). Projections from the LC innervate the caudal raphe nuclei, which are thought to affect sympathetic function via serotonergic output. Sympathetic nervous system activity is also associated with an alert state, whereas increases in parasympathetic activity are associated with decreases in alertness, possibly indicating a role for the serotonergic system in regulating alertness (Lok et al., 2018).

Moreover, DR serotonergic neurons fire extensively during awake periods, while decreased firing rates occur in periods of sleep. Firing rates might, therefore, be linked with

wakefulness and alertness promotion. The SCN, VLPO, LC, and DR pathways described above, might be involved in NIF responses caused by light and, in particular, effects of light on alertness (Hattar et al., 2006; Lok et al., 2018; Vandewalle, Maquet, et al., 2009).

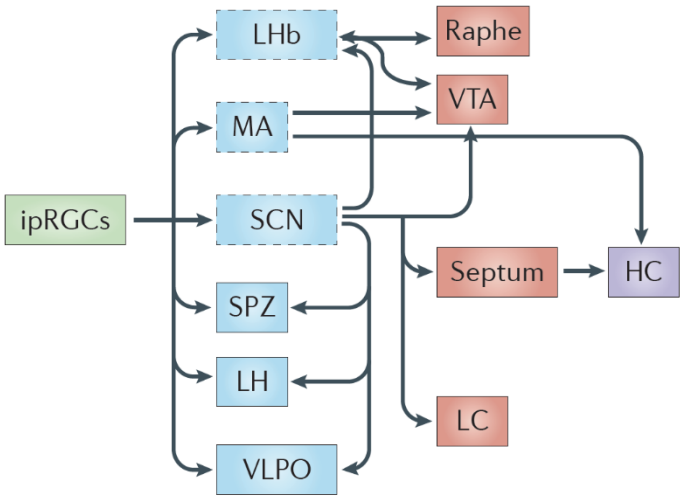

Fig 4. Brain circuits underlying the effects of light on NIF visual functions. Several of the ipRGC targets, including the SPZ (subparaventricular zone), VLPO (ventrolateral preoptic area), LH (lateral hypothalamus) and LHb (lateral habenula), also receive innervation from the SCN, raising the possibility that aside from its pacemaker function, the SCN can also act as a conduit for light information. Areas involved in mood regulation (VTA (the ventral tegmental area) and raphe) and cognition (HC (the hippocampus)) can be influenced by light either through the SCN or in parallel through the MA and LHb. Adapted from (LeGates et al., 2014).

A recent series of neuroimaging studies aimed to identify how brain activity related to ongoing (non-visual) auditory tasks is modulated by light exposure. The first study used Positron Emission Tomography (PET) to investigate the effects of light at night (Perrin et al., 2004). The three other experiments used functional Magnetic Resonance Imaging (fMRI) to detect the effects of light exposure during the day; after all, being a diurnal species, it is during the day that humans are most exposed to light and engage in cognitive tasks (Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle, Schmidt, et al., 2007). Light-induced modulations of brain activity while participants are engaged in non-visual cognitive tasks were detected in numerous areas including alertness-related subcortical structures such as the brainstem, in a location compatible with the locus coeruleus (LC); the hypothalamus, in a location encompassing the SCN; and dorsal and posterior parts of the thalamus, but also in long-term memory and emotion-related areas such as the hippocampus and amygdala. At the cortical level, such modulations were detected in areas involved in the top-down regulation of attention such as the dorsolateral prefrontal cortex, intraparietal sul-

cus (IPS) and superior parietal lobule, as well as in areas involved in the bottom-up reorientation of attention including the right insula, the anterior cingulate cortex, and the superior temporal sulcus. Light-induced activity modulation was also detected in the left frontal and parietal cortices typically implicated in working memory (middle frontal gyrus, supramarginal gyrus, and IPS). Furthermore, modulation of activity was also detected in other areas typically engaged by the oddball task such as the precuneus, posterior cingulate and fusiform gyrus (Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle, Schmidt, et al., 2007). Thus, the first important feature of the modulation of ongoing cognitive processes by non-visual effects of light is that it is triggered in widespread sets of subcortical and cortical regions (see Fig. 5) encompassing different cognitive functions.

The non-visual modulation of brain activity elicited by cognitive processes is, therefore, wavelength-dependent, with a pre-eminence of blue light in eliciting these effects for exposure durations ranging from a few seconds to about 20 minutes. In accord with animal research, results of these studies confirm that light firstly influences subcortical structures involved in arousal regulation, before significantly affecting the cortical areas involved in the ongoing cognitive processes (Gaggioni et al., 2014; Vandewalle, Maquet, et al., 2009).

3.2 Procognitive effect of light

Melanopsin-expressing ipRGCs project to various brain regions, including hypothalamic, thalamic, striatal, brainstem, and limbic structures. Importantly, ipRGCs also directly project to the SCN. These widespread and numerous projections are a crucial feature of the brain mechanisms through which light can exert potent and diverse effects on NIF functions (Gaggioni et al., 2014). As mentioned earlier, light can affect sleep, wakefulness, and cognition indirectly, via its synchronizing/phase-shifting effects on the circadian clock. Also, light conveys a direct stimulating signal that affects sleep homeostasis (Altimus et al., 2008; Chellappa et al., 2013) and increases cognitive performance (Cajochen et al., 2005; Rahman et al., 2014). In humans, circadian rhythmicity influences numerous cognitive processes including attention, working and declarative memory as well as executive functions (Cajochen et al., 2011; Gaggioni et al., 2014; Rahman et al., 2014; Rodriguez-Morilla et al., 2017; Slama et al., 2015; Vandewalle, Maquet, et al., 2009) or decision-making processes (Alkozei et al., 2016). Typically, circadian rhythms in cognitive performance are characterized by a progressive decline in performance during the biological night and a progressive improvement during the biological day.

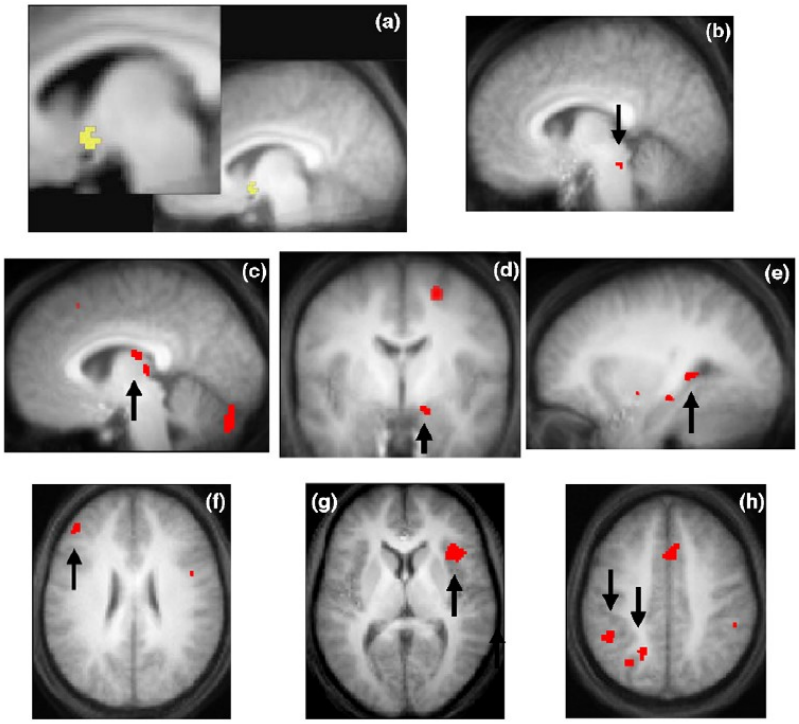

Fig 5. Brain areas in which light elicited modulation of regional activity. Regional activity, as detected by either PET (a) or fMRI (b–h), during non-visual cognitive tasks. (a), hypothalamus, (b) brainstem including LC, (c), thalamus, (d), amygdala, (e), hippocampus, (f) middle frontal gyrus, (g) insula, (h) parietal cortex (supramarginal gyrus and intraparietal sulcus). Adapted from (Vandewalle, Maquet, et al., 2009).

Light can affect cognitive performance through its synchronizing/ phase-shifting effects on the circadian clock. Thus, prolonged night-time bright light exposure and modifications of sleep-wake schedules can alter the timing of the rhythm in cognitive performance. Light can also affect cognitive performance through direct activating effects. It was indeed shown that performance improves acutely after the onset of light exposure, both at night (Cajochen et al., 2000; Lockley et al., 2006) and during the day (Phipps-Nelson, Redman, Schlangen, & Rajaratnam, 2009; Ruger et al., 2006), typically within 30 minutes. Such performance-enhancing effects have been shown for visual search, digit recall, serial addition-subtraction, two-column addition, logical reasoning task, letter cancellation task, and simple reaction time tasks. Standard electroencephalogram (EEG) and ocular correlates of alertness and attention have been shown to covary to some extent with performance. For example, EEG alpha (8–12 Hz) and beta activity (20–30 Hz) show a pronounced circadian rhythm with a peak in the second half of the biological day (Cajochen, Wyatt, Czeisler, & Dijk, 2002). Light exposure reduces alpha, theta, and low-frequency activity, which are correlates of sleepiness (Cajochen et al., 2000; Lavoie, Paquet, Selmaoui, Rufiange, & Dumont, 2003; Lockley et al., 2006). Furthermore, light exposure also reduces the incidence of slow eye

movements, which are indicators of inattention that increase in response to sustained wakefulness, especially during the biological night (Gaggioni et al., 2014).

Exposure to blue-enriched light during the post-lunch dip period reduced the alpha EEG activity and increased task performance. Since the desynchronization of alpha activity reflects the enhancement of vigilance, these findings imply that blue light might disrupt the post-lunch dip (Baek & Min, 2015).

Event-related potential (ERP) study by Okamoto and Nakagawa (Okamoto & Nakagawa, 2015) point to an alerting effect of shorter-wavelength light by means of an increase in P300 amplitude. A study by Lin et al. (Lin, Westland, & Cheung, 2019) evaluated the acute alerting effects of short-wavelength light of three different intensities (40, 80, and 160 lux). EEG beta was significantly higher after exposure to 160 lux light than after exposure to 40 lux, 80 lux light, or dark condition. Also, the alpha-theta power was significantly lower under 160 lux light than in dark condition. These results indicate that the effect of intensity on alertness is not linear, and further research should investigate the threshold intensity that is needed to produce alerting effects. The effects of luminance on CNV (the contingent negative variation) and spontaneous EEG during 10 min of simple reaction tasks were also measured, and an inverted-U shape relationship between the changes in arousal level by light stimulation and CNV was identified (Higuchi et al., 1997). Noguchi et al. (Noguchi et al., 1999) also showed that the proportion of alpha EEG activity fell markedly on > 3 lux illuminance conditions as compared to lower illuminances. The effects of changing illuminance on somatosensory evoked potential (SEP) and subjective sensory evaluation were also examined. Yoshinaga et al. found that the SEP amplitude and the subjective sensory evaluation decreased when illuminance was lowered and increased when illuminance was raised (Katsuura & Lee, 2019; Yoshinaga et al., 2011). On the other hand, Domagalik et al. (Domagalik, Oginska, Beldzik, Fafrowicz, & Marek, 2019) have shown that reducing the transmittance of blue light by approximately 90% for the period of four weeks leads to a decrease in performance in sustained attention and visuospatial memory in healthy volunteers.

A few more ecological studies focused on the effect of shorter-wavelength light in nonlaboratory conditions. For example, blue-enriched polychromatic light in an office environment facilitates alertness, higher performance, and higher sleep quality during the following night (Ferlazzo et al., 2014), while using blue-enriched polychromatic lights in classrooms increases cognitive processing speed and concentration (Keis, Helbig, Streb, & Hille, 2014).

Daytime lighting conditions did not affect intensive care unit nurses' cognitive performance, perceived depressive signs and symptoms, or fatigue. Perceived quality of life, predominantly in the psychological and environmental domains, was lower for nurses working in blue-enriched dynamic lighting (Simons et al., 2018).

Compared to office workers receiving low levels of circadian-effective light in the morning, receiving high levels in the morning is associated with reduced sleep onset latency (especially in winter), increased phasor magnitudes (a measure of circadian entrainment), and increased sleep quality. High levels of circadian-effective light during the entire day are also associated with increased phasor magnitudes, reduced depression, and increased sleep quality (Figueiro et al., 2017).

Several studies have compared the alerting effects of short-wavelength light to caffeine. Beaven and Ekstrom (Beaven & Ekstrom, 2013) showed that both the caffeine only and blue light only conditions increased accuracy in a visual reaction test, and an additive effect was observed with respect to the fastest reaction times. Furthermore, the effect of blue light exceeded the effect of caffeine when both congruent and incongruent distractions were presented. The visual reactions in the absence of a decision or distraction were also enhanced in the blue light only condition. Taillard et al. (Taillard et al., 2012) compared blue-light and caffeine in volunteers in a night-time driving scenario. They showed that both caffeine and blue-light resulted in a reduced number of inappropriate line crossings. Results also showed that countermeasures significantly reduced the number of inappropriate line crossings as compared to placebo (caffeine-free coffee). These results suggest that this in-car countermeasure could be used to fight nocturnal sleepiness at the wheel.

In conclusion, while the effects of light on sleep and alertness in humans have been characterized in detail, understanding the role of specific photoreceptors and neural pathways underlying these responses is not fully understood. As the effects of light on these processes in nocturnal rodents such as mice are inconsistent, further research requires valid animal models to properly understand the mechanisms mediating the effects of light on these fundamental processes (Tam, Bannerman, & Peirson, 2020).

3.3 Effects of light on cognition depend on age and PER3 genotype

Aging is associated with measurable changes in the regulation of sleep and wakefulness - sleep becomes shallower, less restorative, and more fragmented, as the amount of SWS decreases (Klerman & Dijk, 2008). The amplitude of the circadian signal is also reduced in aging, as implied by the reduced harmful effect of night-sleep loss at the behavioral

level, but also by earlier awakenings during sleep (Daneault et al., 2014; Gaggioni et al., 2014). Daneault et al. (Daneault et al., 2016) reported that even if present, the impact of light exposure on brain responses was reduced in older healthy individuals (>60 years old), compared to younger individuals (<30 years old), when investigated after habitual sleep time. Reduced impacts of light were observed within the insula, prefrontal cortex, amygdala, tegmentum, and thalamus, the key structures in the regulation of alertness and cognitive functions.

Vandewalle et al. (Vandewalle, Archer, et al., 2011) looked at the relationship between *PER3* genotype and light exposure. The same participants were exposed to changing blue and green light during a 3-back task. Light conditions were specifically chosen to stimulate the NIF photoreception system (blue) or the classical photopic system (green). Their results showed that in the morning after sleep, blue light significantly enhanced brain responses in prefrontal and parietal areas, as compared to green light. These effects of blue light were only found in *PER3*$^{4/4}$ individuals. In the morning session following sleep deprivation, blue light also significantly increased task-related brain activity. This effect of blue light was observed again in the prefrontal and parietal cortices, and also in other regions, including the insula and the pulvinar. Importantly, in the morning following sleep deprivation, these effects of blue light were only observed in *PER3*$^{5/5}$ (Gaggioni et al., 2014; Vandewalle, Archer, et al., 2011).

Also, Chellappa et al. (Chellappa et al., 2012) showed that light sensitivity in humans might be modulated by a clock gene polymorphism implicated in the sleep-wake regulation. When compared to light at 2500 K, blue-enriched light at 6500 K caused significant suppression of the evening rise in melatonin levels in PER3$^{5/5}$, but not in PER3$^{4/4}$ individuals. Likewise, PER3$^{5/5}$ individuals exhibited a more pronounced alerting response to light at 6500 K than PER3$^{4/4}$ volunteers. Waking theta EEG activity (5–7 Hz), a correlate of sleepiness was drastically attenuated during light exposure at 6500 K in PER3$^{5/5}$ individuals as compared with PER3$^{4/4}$. The authors provided the first evidence that humans homozygous for the PER3$^{5/5}$ allele are especially sensitive to blue-enriched light, as indicated by the suppression of melatonin and waking EEG activity (Chellappa et al., 2012).

3.4 Brain mechanisms involved in the interplay between light, cognition, and sleep-wake regulation

The anterior hypothalamus, its SCA (suprachiasmatic area), but also the ORX/MCH posterior LH, constitute areas through which the circadian and homeostatic processes interact and regulate cognitive brain activity (C. Schmidt et al., 2009; C. Schmidt et al., 2012). The hypothalamus can also be considered one of the first structures affected by light, within the SCA (Perrin et al., 2004), but also possibly in other nuclei such as the PVNH, dorsomedial hypothalamus (DMH) or LH in the emotional task context (Vandewalle, Hebert, et al., 2011; Vandewalle et al., 2010). Also, the hypothalamus, and the SCN in particular, is indirectly connected with the locus coeruleus, a region of the brainstem that is the primary source of norepinephrine (Aston-Jones, 2005) and is likely to be the region influenced by light in nonvisual scenarios (Vandewalle, Schmidt, et al., 2007). Both structures are implicated in the regulation of sleep and wakefulness and have multiple connections to other relevant brain regions, including the thalamus and cortex for the LC. Therefore, the hypothalamus and LC could be the subcortical core area that controls the circadian alerting signal and the stimulating impact of light (Gaggioni et al., 2014). For more challenging cognitive scenarios (e.g., late evening hours, sleep deprivation, or higher-order executive tasks), cortical areas seem to enter into play. When looking at brain responses in the evening, both morning and *PER3*$^{5/5}$ individuals were unable to sustain stable brain responses to cognitive inhibition or working memory tasks (C. Schmidt et al., 2012; Vandewalle, Archer, et al., 2009). Also, when testing working memory in the morning following sleep deprivation, the role of the lateral prefrontal cortex (LPFC) appears critical for maintaining brain responses. *PER3*$^{5/5}$ individuals are unable to maintain activation in DLPFC (Vandewalle, Archer, et al., 2009). By contrast, the activation of the VLPFC in *PER3*$^{4/4}$ under sleep deprivation may indicate a compensatory switch to a more appropriate cognitive strategy (Vandewalle, Archer, et al., 2009). Frontal lobes play a major role in executive functions, with the VLPFC being essential for cognitive control and involvement in complex neurobehavioral processes (Koechlin, Ody, & Kouneiher, 2003). The pulvinar, which was activated more following sleep deprivation in *PER3*$^{4/4}$ individuals, also appears to play a critical role in the ability to face sleep loss and circadian dysregulation and may represent another subcortical region through which circadian and sleep homeostasis interaction affects cognition (Aston-Jones, 2005). This assumption is strengthened by analyses that indicate a significant negative association between the overnight change in task-related pulvinar brain responses and daytime pressure to fall asleep

in everyday life across all the subjects (i.e., irrespective of genotype) (Vandewalle, Archer, et al., 2009).

Furthermore, sleep loss and adverse circadian phase bring a significant reduction of activation across all parts of the cortex in *PER3*$^{5/5}$ individuals. Blue light appears to be effective in maintaining brain responses under these adverse circumstances. On the other hand, *PER3*$^{4/4}$ individuals can trigger endogenous compensatory mechanisms that maintain brain responses in the morning after sleep deprivation, and blue light is, therefore, less beneficial to them (Gaggioni et al., 2014). The non-visual impact of light would provide more benefits to the genotype without the capacity to maintain brain responses endogenously and is more challenged by the circadian and sleep homeostatic conditions. Also, *PER3*$^{5/5}$ individuals are more likely to be morning chronotypes and prefer to be active in the morning hours (Archer et al., 2003), so that in the morning following sleep they would be in ideal endogenous conditions to perform, and could not benefit as much from external light stimulation. *PER3*$^{4/4}$ individuals, which represent approximately half of the general population and are more likely to be evening chronotypes, would benefit more from light exposure in the morning after a night of sleep (Gaggioni et al., 2014). This hypothesis is in agreement with previous studies, which were carried out in the morning (after a normal night of sleep), and found a significant impact of light on brain responses in non-genotyped samples (Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle, Schmidt, et al., 2007).

4 The chronotherapeutic potential of light interventions

4.1 Blocking blue-light

As mentioned earlier, exposure to blue light in the evening during hours that are naturally "dark" can postpone the onset of sleep due to suppression and delay of the release of melatonin. Therefore, controlling light exposure in the evening, especially the chronobiologically most potent short-wavelength light produced by modern-day LED-enriched environments, could make an effective intervention to counter circadian rhythm disturbance. Since neural pathways from the retina to the primary circadian pacemaker in the suprachiasmatic nucleus respond only to short-wavelength light, physiological darkness can be produced by blocking these wavelengths. With regards to the evening and night-time exposure to short-wavelength light, blocking this wavelength spectrum may be beneficial, as initially proposed by several studies (Burkhart & Phelps, 2009; Kayumov et al., 2005; Sasseville, Paquet,

Sevigny, & Hebert, 2006) that show, that blocking blue light before bedtime reduces melatonin suppression and improves sleep quality by restoring a more regular day/night rhythm and thereby stabilizing the circadian system. Sasseville et al. (Sasseville et al., 2006) have shown the ability of blue-light blocking glasses to prevent a decline in melatonin levels after 60 min nocturnal bright light pulse as compared to control group where a decrease of almost 50% was observed in melatonin levels.

A potential role for darkness as a treatment for sleep dysregulation has, therefore, been explored with several options proposed to reduce the harmful effects of light on human sleep. Although RCTs are currently lacking (Lawrenson, Hull, & Downie, 2017), many investigators have shown that blue-light shield eyewear is a feasible and acceptable tool (Perez Algorta et al., 2018) able to reduce sleep and circadian dysregulation (Ayaki et al., 2016; Burkhart & Phelps, 2009; Heo et al., 2017; Sasseville & Hebert, 2010; van der Lely et al., 2015), neuropsychological functioning (Zimmerman et al., 2019) or ameliorating sleep problems associated with mental disorders (Bennett, Alpert, Kubulins, & Hansler, 2009; Esaki et al., 2017; Henriksen et al., 2016; Shechter, Kim, St-Onge, & Westwood, 2018). Other methods, such as software filters (e.g., f.lux®, Iris®, Twilight®) and system features (night or reading modes) reducing the amount of short-wavelength light emitted from screens are freely available for the most used mobile platforms, their research application is, however, very sparse (Heath et al., 2014).

Several studies focused on using amber glasses in patients with sleep disorders. A randomized study of subjects with insomnia demonstrated improvement in sleep quality and mood in individuals wearing blue wavelength blocking glasses, compared with a placebo group (Burkhart & Phelps, 2009). A similar open-label study of attention deficit hyperactivity disorder (ADHD) with insomnia has also demonstrated improved global Pittsburgh Sleep Quality Index scores in the subjects wearing blue wavelength-blocking glasses, as well as improved anxiety (Fargason, Gamble, Preston, Hammond, & Mrs, 2013). Schechter et al. (Shechter et al., 2018) reported improved sleep and quality of life in insomnia patients after wearing amber glasses for 2 hours preceding bedtime. They reported that wake-time was significantly delayed, and mean subjective total sleep time (TST), overall quality, and soundness of sleep was significantly higher in amber vs. clear lenses condition over the 7-day intervention period. Zimmerman et al. (Zimmerman et al., 2019) reported improvements in the cognitive functioning of insomnia patients (better performance on the List Sorting Working Memory task and the Pattern Comparison Processing Speed test), after wearing amber glasses in the evening hours. Consideration of intellectual ability indicated that treatment

with amber lenses “normalized” performance on each test from approximately 1 SD below expected performance to expected performance. Esaki et al. (Esaki et al., 2016) have shown that wearing amber glasses in the evening led to an advance of 78 min in DLMO value and an advance of sleep onset time measured by actigraph by 132 min, suggesting that wearing amber lenses may be an effective and safe intervention for patients with DSPD (delayed sleep phase disorder). Wei et al. (Wei et al., 2013) also show an improvement in sleep quality after blue-light-blocking intraocular lens implantation during cataract surgery. These patients reported significantly better subjective sleep quality, longer sleep, and fewer daytime dysfunctions as measured by PSQI.

Other studies focused on the chonotherapeutic potential of amber glasses in affective disorders. A small trial was also carried out by (Bennett et al., 2009) on a group of women seeking help for postpartum depression. Although statistically insignificant, a trend was observed in the reduction of depressive symptoms in women using amber glasses and lightbulbs blocking short-wavelength light as compared to those using placebo intervention. Another study by Esaki et al. (Esaki et al., 2017) failed to show significant improvements in the sleep of depressed patients after wearing blue-light blocking glasses, although half of the BB group showed a clear improvement in sleep quality. They also reported a trend of a shift to morning type (according to MEQ scores) in the blue-light blocking group and evening type in the placebo group. No significant changes in depressive symptoms were reported in either group. Henriksen et al. (Henriksen et al., 2016) have shown patients with bipolar disorder who were acutely hospitalized and given blue-light blocking glasses in addition to standard medication, improved faster (more significant decline in YMRS scores) than the group of patients who received placebo glasses. Preliminary evidence from a feasibility study by Perez Algorta (Perez Algorta et al., 2018) also shows a trend towards longer sleep, fewer awakenings, and a decrease in hypomanic-type symptoms in those wearing amber glasses.

Potential utilization of amber glasses also covers shift-work schedules. A combined field and laboratory study by Boivin et al. (Boivin, Boudreau, & Tremblay, 2012) has also evaluated the use of amber goggles at sunrise in police officers working seven consecutive night shifts as a part of a rotating schedule. Aside from goggles, they were also provided an intervention consisting of intermittent exposure to wide-spectrum bright light at night. The authors conclude that these interventions led to a better physiological adaptation to shift schedule compared to the control group. Similar are also the results of another pilot study (Sasseville & Hebert, 2010) where authors describe and improvement in sleep parameters, subjective vigilance, and performance during an experimental condition when sawmill shift

workers wore blue-light blocking glasses after their night shifts. A study by Rahman et al. (Rahman et al., 2013) also suggests that filtering short-wavelengths may be an approach to reduce sleep disruption and improve performance in rotating-shift workers. Morning use of such glasses in permanent night-shift workers resulted in longer sleep, improved daytime sleep efficiency, and reduced sleep fragmentation (Sasseville, Benhaberou-Brun, Fontaine, Charon, & Hebert, 2009). An interesting study by Figueiro et al. (Figueiro, Sahin, Wood, & Plitnick, 2016) showed that instead of blocking short-wavelength light, using red light improved measures of alertness, and also improved certain types of performance at night without affecting melatonin levels. Their findings could have significant practical and could help rotating shift-workers maintain nighttime alertness, without suppressing melatonin or changing their circadian phase.

More studies have also focused on a healthy population. Van der Lely (van der Lely et al., 2015) used blue blocker glasses as a countermeasure for alerting effects of evening screen exposure in teenagers. They observed that blue-light blocking glasses significantly attenuated LED-induced melatonin suppression in the evening and decreased vigilant attention and subjective alertness before bedtime. They further also confirmed that even the relatively low-level light exposure of LED screens is sufficient to suppress the evening melatonin rise and that amber glasses prevent this light-induced suppressing effect also in adolescents, without changing sleep parameters. Ayaki et al. (Ayaki et al., 2016) have investigated sleep quality and melatonin levels in adults who wore blue-light shield eyewear 2 hours before sleep while using a media device. They also found significantly higher melatonin secretion, higher sleep efficacy, shorter sleep latency, and greater sleepiness during portable device use compared to those wearing control eyewear. Heo et al. (Heo et al., 2017) investigated changes in serum melatonin levels, cortisol levels, body temperature, and psychiatric measures with a randomized, double-blind, cross-over, placebo-controlled design of two 3-day admissions. The use of blue-light-enabled smartphones was associated with significantly decreased sleepiness and confusion-bewilderment and increased commission error. Also, users of blue-light-enabled smartphones experienced a longer time to reach dim light melatonin onset and had increases in body temperature, melatonin levels, and cortisol levels, although these changes were not statistically significant.

Restricting blue-light in the evening has recently been also shown to improve sleep in recreational athletes (Knufinke, Fittkau-Koch, Most, Kompier, & Nieuwenhuys, 2018). Their results indicate that blocking short-wavelength light in the evening, as compared to habitual light exposure, significantly shortened subjective sleep onset latency, improved

sleep quality, and increased alertness the following morning. Restricting mobile phone use before bedtime for four weeks was effective in reducing sleep latency, increasing sleep duration, improving sleep quality, reducing pre-sleep arousal, and improving positive affect and working memory (He, Tu, Xiao, Su, & Tang, 2020).

It might also be assumed that blue-light blocking glasses affect the strength of light as a zeitgeber on circadian physiology by primarily acting on its amplitude rather than on its phase. An enhanced circadian amplitude due to clear light-dark signals favors a proper internal synchronization of multiple circadian processes in the body as well as a consolidated sleep-wake cycle and may positively affect health and well-being (van der Lely et al., 2015). Amber lenses, therefore, represent a safe, affordable, and easily implemented chronotherapeutic intervention for those with circadian misalignment of various etiologies. Possible disadvantages of blocking short-wavelength visible light lie mainly in disturbances of color perception and decreased scotopic sensitivity (leading to a worse performance in dim light conditions) (Lawrenson et al., 2017).

4.2 Dawn simulation

Several studies have also reported using artificial dawn to simulate light conditions to those of a naturally occurring sundown (gradually increasing illuminance and/or increasing the number of short-wavelengths in light) (Faulkner, Bee, Meyer, Dijk, & Drake, 2019). First dawn simulation studies were aimed at improving depressive symptoms in patients with seasonal depression (Avery et al., 1993; Avery, Bolte, Wolfson, & Kazaras, 1994; Terman & Terman, 2006), concluding that using dawn simulation may be as effective as a bright light in treating depressive symptoms, but with lower illuminances used (250lx vs. 4300lx in a study by Danilenko & Ivanova (Danilenko & Ivanova, 2015)). Other studies show that dawn simulation may also be used as an effective tool to improve cognitive performance. Tonetti et al. (Tonetti et al., 2015) showed an improvement of alertness in adolescents, Gabel et al. (Gabel et al., 2015) showed that dawn-simulation light enhances performance in motor tracking task, sustained attention to response task and a working memory task and improves reaction time under conditions of mild sleep restriction.

In another study by Gabel et al. (Gabel et al., 2013), dawn simulation led to improved mood and well-being after sleep restriction, with minimal impact on the circadian phase. Viola et al. (Viola et al., 2015) also reported a significantly gradient reduction in heart rate during the transition from sleep and an increase in cardiac sympathovagal control when artificial dawn was used in healthy subjects. Their data demonstrate that enhancing the wake-

up process by dawn simulation can significantly reduce the deleterious sleep-to-wake evoked cardiac modulation under conditions of increased sleep pressure. Light exposure, which closely resembles natural lighting in the morning, may, therefore, also act as a potential protector for cardiac vulnerability in the critical morning hours.

A study by Bromundt et al. (Bromundt et al., 2019) explored the effect of artificial dawn-dusk simulator light in dementia patients, where circadian desynchronization often occurs due to loss of neuronal function of SCN and/or weakness of external zeitgebers. They found that exposure to this light led to a significantly better mood in the morning hours after waking, higher quality of light, greater alertness, and circadian rhythm stability. They conclude that continuous, long-term application of dawn-dusk simulation at the sleep-wake transitions appears to increase external zeitgeber strength in institutionalized patients with dementia, providing an effective, non-invasive tool to improve mood and ameliorate patients' quality of life.

4.3 Blue-light hazard

In modern society, digital electronic devices are ubiquitous in both the workplace and domestic environments. Driven by requirements for brighter and lower-energy lighting, the last years have seen important changes in lighting for both commercial and home applications, with the increased use of compact fluorescent lamps (CFL) and high-intensity light-emitting diodes (LEDs). With the high number of hours per day that most people spend viewing screens at short distances, it is not surprising that up to 90% of individuals often experience asthenopic symptoms including headaches, eyestrain, ocular discomfort, dry eyes, diplopia, and blurred vision – together called digital vision syndrome or digital strain (Lawrenson et al., 2017). As it is a multifactorial condition with several potential contributory causes, the role played by blue-light in these symptoms may be difficult to extricate (Wu, Seregard, & Algvere, 2006). Although the light emitted by LEDs appears white in color, their emission spectra show peak emissions at wavelengths that correspond to the peak of the blue-light hazard function (Moon et al., 2017).

Studies have shown that exposure of cultured RPE (retinal pigment epithelium) cells to light equivalent to that emitted from mobile screens causes increased free-radical production, reduced cell viability and decreased photoreceptor responses to light. This has led to concerns that the cumulative exposure to blue-light may induce retinal toxicity and increase the risk of age-related macular degeneration (Tosini, Ferguson, & Tsubota, 2016). Studies in animal models and cell cultures have shown that wavelengths in the blue portion of the

electromagnetic spectrum can induce phototoxic retinal damage, with cellular disruption occurring initially in photoreceptors, followed by the RPE. A disruption can also occur after shorter, high-intensity light exposures.

Therefore, the rationale for the introduction of blue-blocking interventions would be not only to prevent the negative impact on the circadian system but to mitigate the risk of retinal toxicity as well as reduce eye fatigue and eye strain too. Indeed, studies show that functional visual responses are more conserved, retinal structure better kept, and photoreceptor survival is higher when blue-light-blocking measures are implemented (Vicente-Tejedor et al., 2018). However, a study by Palavets et al. (Palavets & Rosenfield, 2019) argues that there is currently little evidence to support the use of blue-light blocking filters to minimize near work-induced asthenopia.

4.4 Blue-light and cancer risk

Another important topic related to blue-light exposure and melatonin suppression to consider is a potential cancer risk. No doubts that ALAN (*artificial light at night*) caused the most dramatic environmental change in the last decades and satellite images of human activity increasingly show more places worldwide are illuminated with an increase in light intensity, known today as light pollution. The American Medical Association (AMA) in 2012 passed a resolution about the light at night as a source of pollution, as it suppresses melatonin production and interrupts with our sleep and daily rhythms (AMA, 2012). Although the association between ALAN and cancer development remains somewhat controversial, the current evidence from epidemiological and experimental studies regarding the negative effect of light pollution on human health is worrying greatly (Haim & Zubidat, 2015; Y. Cho et al., 2015). AMA itself calls (AMA, 2012), we should look for healthy illumination that does not interfere with our biological clock (Haim & Zubidat, 2015).

Evidence has been accumulating that there is a link between a lack of melatonin and cancer, especially breast, ovarian, and prostate cancer (Alpert, Carome, Kubulins, & Hansler, 2009). Aside from the sleep-wake cycle, melatonin strongly regulates numerous vital functions, including antioxidant, antiaging, and most relevant anti-oncogenic properties (Srinivasan et al., 2011). The protective features of melatonin against carcinogenic activity are varied and include inhibition of cell proliferation, induction of apoptosis, enhancing anti-tumor immune responses, and inhibition of cancer cell metabolism. The cellular mechanism by which melatonin contributes to cancer prevention is not entirely known, but several epi-

demiological and experimental studies have recurrently suggested a potential role of melatonin in the treatment of cancer (Mediavilla, Sanchez-Barcelo, Tan, Manchester, & Reiter, 2010). Accordingly, the ALAN-induced melatonin suppression stimulates oncogenes and inhibits tumor suppressor genes by genomic regulation of aberrant DNA methylation resulting in tumor progression (Haim & Zubidat, 2015). A study by Kloog et al., for example, showed a 30–50% higher risk of breast cancer in the highest LAN exposed countries compared to the lowest LAN exposed countries. These findings provide coherence of the previously reported case-control and cohort studies with the co-distribution of LAN and breast cancer in entire populations (Kloog, Stevens, Haim, & Portnov, 2010). This information led to the hypothesis that wearing amber glasses before bedtime to maximize melatonin production may also reduce the risk of circadian rhythm disruption and the risk of breast and other cancers (Alpert et al., 2009; Mortazavi & Mortazavi, 2018).

Aside from cancer, sleep disturbance due to ALAN exposure may also have an impact on aging and metabolic processes, as well as on heart disease, diabetes, mood disorders, and obesity (Park, White, Jackson, Weinberg, & Sandler, 2019), which have become pandemic. Therefore, ALAN exposure increases public health concerns in modern societies (Y. Cho et al., 2015). Further studies are warranted to characterize the ALAN spectral threshold for triggering carcinogenetic activity and to implement effective countermeasures for reducing any potential side effects of the novel lighting technology.

5 Possible avenues of lighting research in the future

5.1 Current perspectives and considerations

The idea that blue light exerts a powerful alerting effect opens important avenues for both medical and broader societal applications. Light is currently used as a therapeutic tool, with an efficiency well-established for medical conditions such as circadian rhythm sleep disorders, seasonal affective disorders, and other depression subtypes. Stimulating alertness or maintaining sleep using different wavelength compositions may lead to additional indications of light therapy as a complementary and innocuous treatment to help patients with insomnia, excessive daytime sleepiness, or other psychiatric symptoms (Blume et al., 2019; Bourgin & Hubbard, 2016). Considering societal implications, with the development of LED and progressive switching from fluorescent or other light devices to this newer technology, we are increasingly exposed to non-homogeneous spectra of light. Thus, the possibility to balance light wavelength composition in favor of alertness or sleep maintenance would allow

the adaptation of our illuminated surroundings to our needs, with reservation to the fact that light can also have indirect effects through phase shifting of circadian rhythms. This type of spectral management could be applicable to many daily living conditions, far beyond simply the workplace or the home, allowing us to also better adapt to situations like transmeridian travel or shift-work, in addition to dealing with increasingly continuous screen exposure using modern media and other concomitants of life in modern society (Bourgin & Hubbard, 2016).

As proposed by Katsuura and Lee (Katsuura & Lee, 2019), one of the main goals of future lighting research should be to build a truly adapted artificial environment based on the biological characteristics of human beings, supporting choices for using low color temperature lights in living rooms and bedrooms, and suggested the appropriate timing for light exposure to achieve sleep improvements and healthy life. Furthermore, research results can also be used to define the wavelength of illumination and the transparency characteristics of the eyeglasses needed to achieve enough adaptability for daily activities. Once further knowledge is obtained, the potential applications of this research in daily life may be enormous (Katsuura & Lee, 2019).

Future studies on light-induced impacts of circadian rhythm should clearly indicate the details of the experimental protocol and the subjects. Particular attention shall be paid to the sample size and repeated measure design, as individual differences in melatonin levels were found in many studies. Also, systematic reviews on other light-induced health concerns are needed, as well as meta-analyses of any adverse health impacts, including circadian rhythm disruption, to further clarify the scientific evidence on impacts of light on human health (Tahkamo, Partonen, & Pesonen, 2019). From the review by Souman et al. (Souman, Tinga, Te Pas, van Ee, & Vlaskamp, 2018), it also shows that, though people often report feeling more alert with bright or high CCT light, it is unclear whether and when these effects translate into changes on performance measures of alertness. One reason for this may be that performance on these tasks is determined by multiple factors, of which arousal state is only one. Also, ignoring other factors that influence the effects of light, such as chronotype, circadian phase, homeostatic state, prior light history, and genetic disposition, may obscure its effects on sleep and cognition. Future studies should, therefore, keep better track of these factors and take them into account when evaluating the effects of light exposure. Thus, though periodic exposure to light is essential for our health and wellbeing, the circumstances under which light exposure may enhance or support our functioning still need to be more clearly delineated.

5.2 Biodynamic lighting

Currently, bedroom lighting design standards in clinics exclusively aim at fulfilling visual needs and thus only specify horizontal illuminance levels for ambient and zonal bed lighting. In contrast, the amount of light entering the eyes determines non-visual light effects, but no lighting design practices for non-visual light effects in clinics are presently available. Not only active chronotherapeutic approaches but an adequate architectural design of the light environment as well, may have relevant therapeutic implications for psychiatric patients (Blume et al., 2019). The availability of light in hospital rooms has been indicated to shorten the stay of depressed patients in a clinic (Beauchemin & Hays, 1996). Moreover, retrospective analyses revealed a three-day shorter hospitalization in bipolar depressed patients exposed to natural light in sunny hospital rooms compared to darker rooms (Benedetti, Colombo, Barbini, Campori, & Smeraldi, 2001). A recent Danish study also found that depressed patients admitted to south-east facing rooms were discharged earlier compared to patients in rooms facing north-west (Gbyl et al., 2016). This indicates that natural daylight may be a factor for improvement.

Studies, where blocking blue-light is used to ameliorate psychiatric symptoms were mentioned in the previous chapter. Still, most of these trials have been small and/or in homogeneous samples, and have required the participants to adhere to the study protocol at specified times of the day (e.g., resting in forced darkness or wearing glasses). However, given the prevalence of disturbances of the sleep-wake cycle in individuals with psychiatric disorders, it would be meaningful to extend trials of the use of such interventions to broader trans-diagnostic populations. As suggested by Scott et al., to further increase generalizability, it would help to avoid giving personal responsibility for the timing of their exposure to different characteristics (intensities or spectra) of light to individuals who are acutely mentally unwell (Scott et al., 2019). They suggest a pragmatic alternative, to create an environment where changes in light exposure could be regulated automatically and where programmable lighting conditions would form an integral part of a hospital unit. New LED lights can be programmed to emit lower levels of blue-light, which would create a blue-depleted light environment in the hospital. This might be an intriguing option as, to date, very little consideration has been given to how contemporary technological advances might be used to augment the acute treatment in inpatient facilities (Scott et al., 2019).

Two studies so far (Okkels et al., 2020; Scott et al., 2019) have focused on creating a „circadian-friendly“ LED lighting system in a psychiatric ward. These studies aimed to compare standard hospital lighting with tunable lighting adjusted for intensity, color, and

circadian timing. Scott et al. (Scott et al., 2019), for example, used following settings: at 18:00, the lighting undergoes a 30-minute transition during which the green and blue LEDs are dimmed to produce blue-depleted amber-colored lighting. At 06:50, a 10-minute transition program changes the light color to standard indoor lighting (3000K CCT), which then continues until 18:00. The light intensity is dimmed to 20% (of the maximum) from 23:00 to 06:50. No results have been provided so far as the given data come from a published trial protocol. A study by (Okkels et al., 2020) used a similar lighting system and found no differences as compared to the original hospital lighting. They conclude, however, that the circadian lighting environment was safe and well-tolerated by patients and integrated well with routine clinical care.

A study by Canazei et al. (Canazei et al., 2019) shows that an adjustable dynamic light may alter indoor light exposure patterns in bedrooms of a maternity ward. Under standard light, mothers stayed under low indoor light levels during the day, and by turning room lights on in the evening, they were exposed to enhanced light levels before sleep. In contrast, under dynamic light mothers stayed under increased light levels in the automatic lighting control period in the morning, and when allowed to adjust intensity levels, they chose higher light levels during the daytime and lower evening light levels. This light exposure pattern created a good starting point for the generation of non-visual light effects. However, although they could observe first light effects on neonatal physical activity, maternal sleep, mood, motor behavior, and urinary melatonin levels were unaffected.

In an intervention research project by Engwall et al. (Engwall, Fridh, Johansson, Bergbom, & Lindahl, 2015) a lighting system was set up in an intensive care unit (ICU) room to support patients' circadian rhythm. The lighting system aimed to simulate natural light regarding localization, brightness, and colors of light worked in 14 different light scenes that were all controlled automatically by software round the clock. In the morning, a warm, low-level light started the day and with a continued brighter morning period that aimed to wake and alert the patients. At noon the levels became lower, and daylight shone through the windows. In the afternoon, the lighting levels were higher again, and in the evening, the same warm color and low-level lighting as in the morning were repeated. The results showed the effect of the lighting system on the perception of daytime brightness. Nearly all enrolled ICU patients were pleased with the cycled lighting environment, which, together with daylight, supported their circadian rhythm (Engwall et al., 2015).

Figueiro et al. (Figueiro et al., 2019) aimed to use tailored lighting intervention (TLI) in participants with moderate to late-stage dementia. Participants were exposed to 2 different

daytime lighting conditions: an active lighting intervention providing high circadian stimulus (CS) and a control intervention that provided low CS (i.e., below the threshold for activation of the circadian system). In short, the TLI was designed to deliver targeted levels of circadian light and CS, based on measured nocturnal melatonin suppression. It aimed to affect the circadian system maximally and improve sleep quality, depression, and agitation behavior in participants with moderate to late-stage dementia. They demonstrate that exposures tailored to maximally entrain the circadian system, especially when carefully delivered and measured, can significantly improve sleep quality, depressive symptoms, and agitation in patients with dementia. The light was also well tolerated by the participants, which is essential for the effective delivery of a lighting intervention in real-world applications.

A study by (Hartstein, Tuzikas, & Karlicek, 2019) sought to explore how rapid, dynamic changes in light SPD (spectral power distribution) can impact cognitive performance and comfort compared to traditional, static indoor light fixtures. In this study, static lighting and a dynamic lighting condition consisting of fluctuations in light correlated color temperature (CCT) and constant illuminance were compared. Their data suggest that a degree of unpredictability in the frequency of light CCT changes may be less disruptive to performance and focus than regular, cyclical changes. These preliminary findings highlight the need for future research into how changes in the lighting environment might influence occupant performance and comfort.

A recent review (Faulkner et al., 2019) supports the use of morning light exposure to advance sleep timing and hasten sleep onset in delayed sleep phase disorder. Interventions altering light exposure may help improve sleep continuity or sleep disturbance in groups with circadian dysregulation; appropriate light schedule alterations will depend upon the group. Enhancing evening darkness to promote sleep may be useful; the evidence is as yet weak, but side effects are few. Faulkner et al. (Faulkner et al., 2019) also provide suggestions for future research of light interventions in a clinical population, such as altering light-dark exposure patterns over the whole day or during multiple periods, focusing on evening light avoidance/reduction, reporting season of intervention delivery; and considering individual participant's baseline light exposure patterns.

5.3 Metamerism

In the context of visual displays, there is a basic conflict between the need to produce pleasing image quality and the wish to control physiological impacts of screen exposure.

The inclusion of melanopsin in the pathways that regulate many of these physiological functions, however, raises the exciting prospect of modulating reflex/subconscious light responses without altering visual appearance by using the concept of metamerism (Allen et al., 2018; de Zeeuw et al., 2019). Metamers are stimuli with divergent spectral power distributions but the same color and luminance. Metamers achieve this effect because each of the cone photoreceptors responds to the total light across a wide range of wavelengths, weighted according to their spectral sensitivity. Therefore, it is possible to make balanced changes in the intensity and wavelength of light without affecting the effective photon flux for any given photoreceptor. The divergent spectral power distributions of metamers exploit this phenomenon by having equivalent effective radiance not just for one but for all three of the human cone photoreceptors (Allen et al., 2018; de Zeeuw et al., 2019).

Data from a recent study (Allen et al., 2018) demonstrate that melatonin onset and subjective sleepiness can be modulated independently of photometric parameters (color and luminance) under a commonly encountered light exposure scenario. They provide the first evidence that the impact of light on alertness and melatonin suppression can be controlled independently of visual experience, and establish a visual display unit capable of achieving this objective. They also found that daytime light exposure significantly decreased objective sleepiness (in the wake EEG), while showing a significant reduction in subjective sleepiness only shortly after light onset. The metameric lighting with a spectral peak closer to the maximum melanopsin sensitivity had the largest alerting response. The reduction of objective sleepiness, depending on the light spectra, was seen most clearly in low-illuminance lighting. Furthermore, de Zeeuw et al. (de Zeeuw et al., 2019) show that increasing light exposure to light levels of >1000 lux may not necessarily decrease sleepiness during the daytime. The most evident effect of light intensity on objective sleepiness was found in a reduction of EEG beta activity in frontal regions. Their results also show that the PLR (pupillary light reflex) may be used as a relatively non-invasive physiological marker, sensitive enough to distinguish between metameric polychromatic white-lighting conditions.

Combined, these findings may have implications for the general public by providing recommendations on how to improve lighting in offices, schools, hospitals, or homes by using metameric light sources where the impact of light on alertness and melatonin supression can be controlled independently of visual experience.

RESEARCH PART

Knowledge gaps, research aims, and hypotheses

The primary objective of this thesis was to further clarify the contribution of the short-wavelengths to the cognition-enhancing properties of light and their potential role in disturbing our sleep. We aimed to explore the effects of narrow-bandwidth (monochromatic) light on the vigilance. We further aimed to test the potential of blue-light filtration when used as an adjunct to a standard psychotherapeutic intervention in insomnia patients. And lastly, our aim was to explore the characteristics of light exposure in the evening and during the night and their role in influencing our sleep and next-day functioning.

Building on available published data, we have decided to carry out three separate studies:

Study 1 - Alerting effects of short-wavelength (blue) light during the day

While the majority of studies in cognitive neuroscience so far have focused on comparing full-spectrum polychromatic light with different levels of CCT and/or intensity, we decided to take a different approach and use monochromatic light sources which allow for more precise detection of the contribution of selected light spectra to alerting effects.

Therefore, this study aimed to compare LED light of three different wavelengths (455nm, 508nm, 629nm) in terms of selected subjective and objective parameters of vigilance. We hypothesized that short-wavelength/blue (455nm) light condition would be superior to green- and red-light conditions, reducing subjective levels of sleepiness, reducing reaction time to visual stimuli, and enhancing brain responses in regions associated with visuospatial attention. Using several electrophysiological measures (spectral analysis, ERP, eLORETA), not applied in previous studies, and objective measures of cognitive processing within the same subjects during cognitive load, we planned to provide further information regarding the alerting effects of short-wavelength light, contributing to future studies and potential applications in lighting or light-filtering technology.

Study 2 - Benefits of blocking blue light in the evening when used as an adjunct to CBT for patients with insomnia

Although the efficacy of CBT-I in the treatment of insomnia has been well studied (C. M. Morin et al., 2006), there is still a certain percentage of patients (19 - 26 %) who do not respond to this type of treatment (Murtagh & Greenwood, 1995). Sleep hygiene, a set of behavioral and environmental recommendations, is a standard part of CBT-I (C. M. Morin et al., 2006); unfortunately, small to none attention is paid to the "light hygiene" – a set of rules and recommendations to mitigate the negative impact of evening/night screen exposure on sleep quality. This would be hypothesized to ameliorate the impact of light on the circadian system by preventing light-induced melatonin suppression, leading to reduced phase-delaying effect of light and decreasing cortical arousal (Rodriguez-Morilla et al., 2017; Sasseville et al., 2006), further enhancing the outcomes of CBT therapy in insomnia patients.

To test this hypothesis, a randomized controlled trial was run to assess the effect of CBT-I in combination with blue-light-blocking glasses (BB glasses) – a simple and easy-to-use intervention to block the adverse effects of evening exposure to blue-light. A CBT-I group with active glasses was compared with a CBT-I group wearing clear placebo glasses. We expected to find improvement in sleep parameters and psychiatric symptoms in both groups with a larger effect in the group with active filtering glasses.

Study 3 - Exploring evening and night exposure to light from media screens and potential benefits of adhering to "light hygiene" recommendations in a healthy population

Incorporating recommendations related to appropriate light exposure into the practices of sleep hygiene may help to advocate a focus on "light hygiene" to promote public health and prevent disease, as initially proposed by Erren & Reiter (Erren & Reiter, 2009). These may include: reducing exposure to artificial light in the evening and night hours, blocking short-wavelength light from electronic sources, exposing oneself to outdoor lighting during the day, or using blue-depleted light sources that do not lead to chronodisruption. Given the prevalence of sleep problems and the widespread use of electronic devices, could a bigger focus on "light hygiene" ameliorate poor sleep and sleep-related symptoms? The following aims have been put forward to test this hypothesis.

This study aimed to test a healthy population for the use of screen-based devices during the evening and night hours and its association with subjectively perceived sleep

quality and other sleep-related parameters. Additionally, we decided to compare groups of participants based on their use of blue-light filters and the amount of time they are exposed to electronic devices throughout the day, 90 minutes before their usual bedtime (which is hypothesized to be especially important because of sensitivity to suppression of melatonin levels) and during the night-time and examine the differences in their subjectively perceived sleep quality. These parameters, as their presence in current literature, is very sparse, are especially crucial for developing future interventions and strategies directly aimed at adhering to sleep (and light) hygiene recommendations with the potential to improve one's sleep. We hypothesized that longer screen exposure times would be associated with worse sleep quality. We also predicted that screen exposure 90 minutes before bedtime would be associated with worse outcomes on all sleep-related measures, while blue-light filtering would be associated with better outcomes.

6. Study 1 – EEG experiment

6.1 Study protocol

The experiment consisted of 3 different sessions and was conducted on three separate days, with a week in-between sessions. The subjects, in a randomized order, were exposed to the light of different wavelengths on each day of the experiment. Experimental sessions consisted of a 10-minute red light adaptation to reach a sensitivity baseline for ipRGCs (as mentioned by Chellappa and colleagues Chellappa et al. (2014)) and a 15-minute dark condition for the adaptation of rods and cones followed by a five minutes-long oddball task also in darkness. After the oddball task, the subject performed a PVT (Psychomotor Vigilance Task (Dinges & Powell, 1985)) on a computer screen (Dell Inspiron 3147) with the brightness at the lowest levels and f.lux filter (https://justgetflux.com/, 2017) turned on for minimalizing the stimulating effects of artificial light (illuminance level <1 lux). After the PVT task, the lightbox was turned on, and the subject went through 3 oddball sessions followed by a 5 min resting-state measurement and a PVT task after switching the lightbox off. The total length of the "under light" session was about 20 minutes, after which the experiment was concluded. In between administered tasks, the subjects were also asked to rate their level of subjective sleepiness using the adapted version of the Karolinska Sleepiness Scale at seven different timepoints during each session. The experiment took place during the post-lunch period, between 12:00 and 15:00. The protocol of the study is depicted in the following figure (Fig 6).

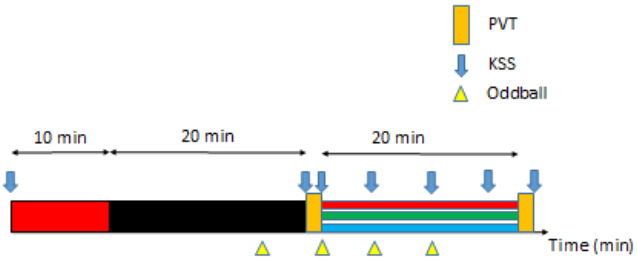

Fig 6. The protocol of the study. Ten minutes of red light (629 nm) ipRGCs adaption followed by 20 minutes of the dark period (rod/cone adaptation), followed by approximately 20 minutes of exposure to one of three experimental lightning conditions. PVT, KSS, and Oddball measurements were conducted, as depicted in the figure.

6.2 Participants

Twelve healthy (8 women and 4 men) volunteers between ages 24 and 32 (mean 27.3 years, SD = 2.38) were recruited and screened for severe neurological, psychiatric, and sleep disorders. The use of medication before the experiment was not allowed. All participants were nonsmokers and were instructed to refrain from consuming caffeine, alcohol, or other cognition-altering drugs during the 12-h period before the experimental sessions. None of them worked night shifts, nor has traveled across time zones in 4 weeks preceding the experiment. To minimize inter-individual variation in the circadian phase, individuals with extreme chronotypes were not accepted into the study.

6.3 Methods

Light exposure: Narrow-bandwidth light with short, medium or long wavelengths was delivered via custom-made lightbox device (Lightbox RGB 500, H. Medřický, LuxVitaEst, Prague, Czech Republic, shown in Fig. 7), 55x50x16cm in size, consisting of 14.4W RGB LEDs located on the sides and an acrylic board placed 30 cm away from the participant's eyes. The light was evenly distributed using a diffuser. The peak wavelengths for the short, medium and long-wavelength lights were 455nm, 508nm, and 629nm (Fig 8). The target irradiance density at the level of the eye was 14 $\mu W/cm^2$ for all light conditions (similar to (An, Huang, Shimomura, & Katsuura, 2009; Okamoto & Nakagawa, 2015)), with illuminance levels of 11.81 (455nm), 15.42 (508nm) and 29.48 lux for 629nm light. The illuminance level of the dark condition was 0.01 lux at the subjects' cornea.

Fig 7. Lightbox used in the experiment.

Fig 8. Lighting conditions used in the experiment (629, 455, 508 nm)

Actigraphy: The objective assessment of sleep and wake patterns was done using a wrist-worn actigraphic device with a tri-axial accelerometer (MotionWatch8, CamNTech, Cambridge, UK, www.camntech.com). The subjects wore the device continuously for three weeks on the non- dominant upper extremity.

Sleepiness and reaction time measurements: Subjective sleepiness was measured by a translated version of the Karolinska Sleepiness Scale (KSS) (Akerstedt & Gillberg, 1990), a 9-point Likert scale based on a self-reported, subjective assessment of the subject's level of drowsiness at the time. KSS scores were taken at seven different timepoints during each experimental session.

PVT (reaction time): After the oddball task in the dark, the subject performed a visual PVT task for the first time and at the end of the experiment (after 20 min of light exposure) for the second time, using the PEBL freeware (version 0.14, available at http://pebl.sourceforge.net/download.html) running the PEBL Perceptual Vigilance task, 20 stimulus trials in total.

EEG and ERP measurements: The subjects were sitting in an upright position in a chair with their eyes open. The EEG signal was registered from 21 Ag/AgCl scalp electrodes fixed on a cap, in positions following the International 10/20 system (Electro-Cap International, Inc., ECI). Two electrooculogram (EOG) electrodes were added to monitor eye movements. Electrode impedances were kept below 5 kΩ. Data was acquired with a BioSDA09 standard 32-channel digital EEG amplifier (M&I Ltd., Prague, Czech Republic), with a bandpass of 0.1 - 200 Hz and was digitalized continuously at a sampling rate of 1000Hz. The stimuli for ERP generation were presented by Presentation® software through Sennheiser HAD 280 headphones.

P300: An auditory oddball paradigm with 120 standard (200 Hz, 40 ms, 75 dB SPL) and 30 target (500Hz, 40 ms, 75 dB SPL) tones were presented binaurally in a pseudo-random order (interstimulus interval, ISI = 1200 ms). The subjects were instructed to keep their eyes open and count in their mind the infrequent higher-pitched target tones in a background of standard stimuli.

Power Spectra and eLORETA analysis: Welch method was used to perform the spectral analysis (frequency range 0.5-50Hz, 1Hz resolution). It divides the signal into overlapping segments and computes a modified periodogram for each segment. The average of these estimates is the estimate of the spectral power density. After recomputation to the average reference, spectral analysis was performed for continuous EEG epochs with the data digitally filtered into six frequency bands: delta (0.5-3.5Hz), theta (4-7Hz), alpha 1 (7.5-9.5Hz), alpha 2 (10-12Hz), beta 1 (13-16Hz and 17-23Hz), beta 2 (24-34Hz) and gamma (35-50Hz) according to the conventional International Federation of Clinical Neurophysiology guidelines (Nuwer et al., 1998).

EEG connectivity analysis has been performed using the exact low-resolution electromagnetic tomography (eLORETA) software (publicly available free academic software

at http://www.uzh.ch/keyinst/loreta.htm). The eLORETA algorithm is a linear inverse solution for EEG signals that has no localization error to point sources under ideal (noise-free) conditions (Pascual-Marqui et al., 2011) and was found to have a slightly increased localization performance compared to the previous sLORETA version.

EEG data preprocessing: All of the data preprocessing was performed in BrainVision Analyzer 2.1 (Brain Products GmbH). Data was filtered with a 0.1–20 Hz band-pass filter, re-referenced to linked mastoids, and segmented in 1-s epochs. Artifacts were detected by visual inspection and rejected employing semi-automatic artifact rejection. Subsequently, after careful inspection by a trained researcher, epochs contaminated by sweat, technical, or continuous muscle artifacts were removed. Artifacts from eye movements or eye-blinks were removed with an independent component (ICA) algorithm.

Statistical Analysis: The IBM SPSS Statistics software (v 23.0) was used for analyses. The effects of light condition and timepoint on change in KSS score were assessed using a two-way repeated-measures ANOVA. For KSS score, a 3 × 4 (3 light conditions × 4 timepoints) repeated measures ANOVA was used. One-way ANOVA was also used for analyzing differences in PVT reaction time and P300 latencies. Power spectrum analysis was performed using the Kruskal-Wallis nonparametric test, followed by Dunn-Bonferroni correction for adjusting to multiple comparisons. A 3 × 3 repeated-measures ANOVA was used for P300 latency and amplitude comparisons. Post hoc multiple comparisons with Bonferroni correction were performed to investigate significant main effects where necessary.

6.4 Summary of results

Subjective sleepiness: Results of the 3x7 (3 light conditions x 7 timepoints) repeated measures ANOVA on mean KSS score (Fig 9) showed that there was a significant main effect of light color ($F(2,249) = 5.178$, $p = 0.006$, Cohen's $f^2 = 0.002$) and timepoint ($F(6,245) = 6.311$, $p<0.001$, Cohen's $f^2 = 0.165$), but no significant effect of interaction ($F(12,252) = 0.298$, $p = 0.989$). Multiple comparisons post-hoc tests detected a significant difference between blue (455nm) and red (629nm) light conditions ($p = 0.005$), indicating that participants were less sleepy under blue than under red light conditions.

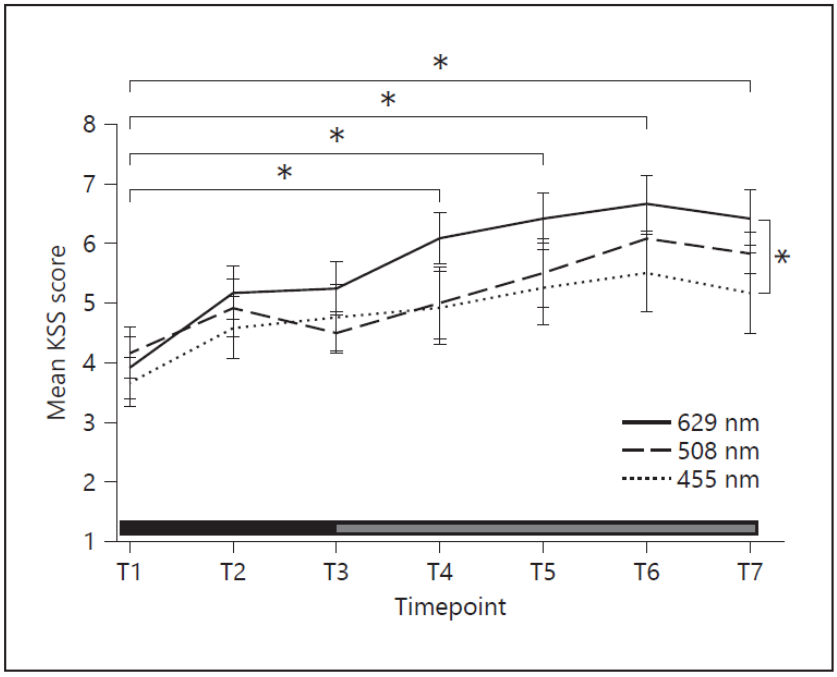

Fig 9. Mean subjective sleepiness as assessed by the translated KSS version. Higher scores indicate higher subjective sleepiness. Stars marks the significant difference between light conditions ($p = 0.006$) and timepoints (all $p < 0.001$). T4 represents the first measurement under light exposure, shortly after completing the first oddball task.

PVT (reaction time): Results from the PVT task were obtained as the difference between the mean reaction time during the dark condition minus the reaction time under light exposure during the same day of the experiment. Results of the One-Way ANOVA show no statistically significant difference between the differential values ($F(2,685) = 2.364$; $p = 0.095$), although an improvement in reaction time can be observed for the green light condition (3.92 ± 64.45 ms) while slower reaction times (RT) were observed under blue (-6.08 ± 62.82 ms) and red (-7.86 ± 59.75 ms) light conditions (Fig 10).

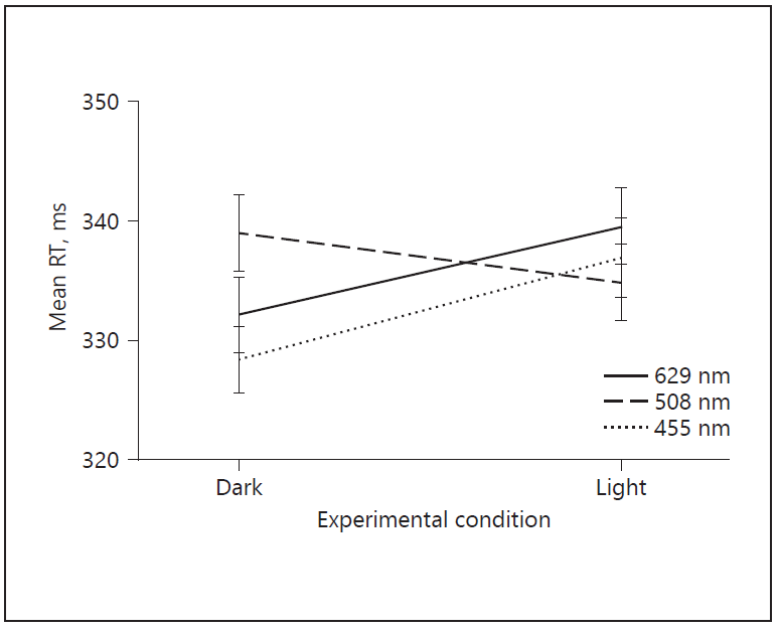

Fig 10. Mean reaction time (RT) during the dark and experimental lighting conditions. No significant differences were found between the differential values (p = 0.095).

Power spectrum analysis: A spectral analysis was carried out for all electrodes in the following frequency bands: delta (0.5-3.5Hz), theta (4-7Hz), alpha 1 (7.5-9.5Hz), alpha 2 (10-12Hz), beta 1 (13-16Hz and 17-23Hz), beta 2 (24-34Hz) and gamma (35-50Hz). The results were obtained as a difference between the absolute spectral power during cognitive load (PVT task) in dark and light conditions. Using the Kruskal-Wallis nonparametric test followed by Dunn-Bonferroni correction for adjusting to multiple comparisons, we found that blue (455 nm) light was the only experimental condition that led to an increase in absolute power. Results from all electrodes are to be found in Table 1, significant results being marked by bold letters.

	0.5–3.5 Hz		4–7 Hz		7.5–9.5 Hz		10–12 Hz		13–16 Hz		17–23 Hz		24–34 Hz		35–50 Hz	
	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p
AFz	2.326	0.313	3.767	0.152	0.032	0.984	1.087	0.581	0.078	0.962	4.734	0.094	4.551	0.103	6.572	**0.037**
C3	4.222	0.121	4.821	0.090	1.581	0.454	3.623	0.163	1.947	0.378	0.839	0.657	5.844	0.054	6.569	**0.037**
C4	1.676	0.433	1.650	0.438	1.195	0.550	1.146	0.564	0.275	0.871	0.137	0.934	2.515	0.284	6.842	**0.033**
Cz	1.483	0.476	0.734	0.693	0.059	0.971	0.920	0.631	0.236	0.889	0.734	0.693	2.128	0.345	5.140	0.077
F3	1.443	0.486	1.842	0.398	1.740	0.419	1.902	0.386	3.659	0.160	1.427	0.490	2.533	0.282	6.650	**0.036**
F4	2.302	0.316	1.659	0.428	2.902	0.234	2.041	0.360	0.560	0.756	3.586	0.166	7.074	**0.029**	5.407	0.067
F7	0.263	0.877	0.920	0.631	4.194	0.123	1.191	0.551	2.542	0.281	0.722	0.697	2.324	0.313	6.695	**0.035**
F8	0.551	0.759	4.114	0.128	0.698	0.705	0.470	0.791	1.488	0.475	0.020	0.990	2.113	0.348	0.650	0.722
Fp1	0.272	0.873	1.218	0.544	2.011	0.366	0.362	0.834	1.195	0.550	1.227	0.542	0.956	0.620	2.601	0.272
Fp2	1.542	0.463	0.168	0.919	0.344	0.842	0.921	0.631	2.596	0.234	2.907	0.234	3.826	0.148	3.407	0.182
Fz	0.254	0.881	1.713	0.425	0.074	0.964	1.095	0.579	0.474	0.789	2.000	0.368	6.245	**0.044**	8.410	**0.015**
O1	2.018	0.365	4.330	0.115	1.135	0.567	1.101	0.577	1.113	0.573	0.114	0.945	2.929	0.231	10.074	**0.006**
O2	1.560	0.458	2.096	0.351	1.686	0.430	1.230	0.541	2.584	0.275	3.977	0.137	2.000	0.368	3.689	0.158
P3	3.173	0.205	0.695	0.706	1.389	0.499	0.150	0.928	0.114	0.945	1.856	0.395	3.815	0.148	2.128	0.345
P4	0.821	0.663	0.344	0.842	0.110	0.947	0.0656	0.720	0.770	0.680	2.186	0.335	1.389	0.499	3.047	0.218
Pz	0.655	0.721	0.342	0.743	0.470	0.791	0.011	0.995	0.290	0.865	0.086	0.958	2.281	0.320	2.024	0.363
T3	8.140	**0.017**	6.632	**0.036**	7.646	**0.022**	5.734	0.057	2.284	0.319	6.529	**0.038**	7.893	**0.019**	6.168	**0.046**
T4	6.505	**0.039**	5.680	0.058	7.749	**0.021**	3.788	0.150	1.743	0.418	3.839	0.147	7.074	**0.029**	6.601	**0.037**
T5	4.992	0.082	4.815	0.090	2.137	0.344	1.545	0.462	0.500	0.779	3.317	0.208	5.640	0.060	6.245	**0.044**
T6	2.182	0.336	1.938	0.379	0.799	0.671	0.119	0.942	0.814	0.666	4.194	0.123	3.718	0.156	6.302	**0.043**

Table 1. Results of absolute EEG power density for all electrodes. The results were obtained as a difference between the absolute spectral power during cognitive load (PVT task) in dark and blue-light conditions. "p" represents adjusted p-value. All significant results point towards higher EEG power density under the blue-light condition as compared to darkness.

ERP P300 Analysis: Three aspects of the P300 component elicited by an oddball task were derived to assess brain cognitive function (amplitude, latency, and area under the curve – AUC). Firstly, we compared latencies of P300 responses (at Fz site) under light and dark conditions. Results in Figure 11 show the difference between latency during the baseline dark measurement and measurement under light conditions. Blue light (455nm) was the only lighting condition where subjects showed an improvement in latency, meaning reacting faster than under the dark condition. Results of the 3x3 (3 light conditions x 3 timepoints) repeated measures ANOVA on mean latency differences showed that there was a significant main effect of light color ($F(2,97) = 3.720$, $p = 0.028$, Cohen's $f^2 = 0.006$) but no significant effect of ERP measurement ($F(2,97) = 0.837$, $p > 0.05$), nor interaction between color and ERP ($F(4,100) = 0.350$, $p > 0.05$).

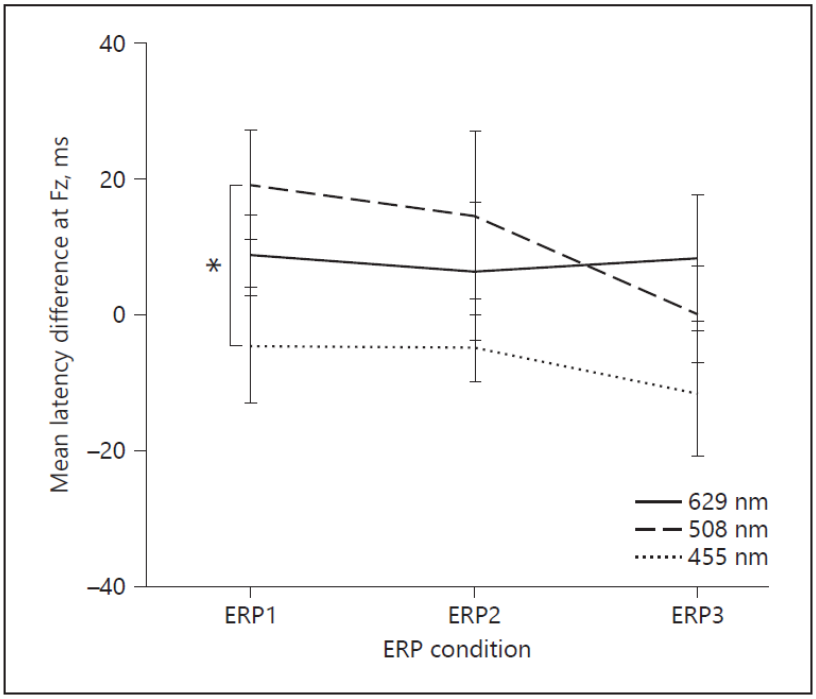

Fig 11. The difference between latencies of P300 response under light and dark condition. Negative values show the decrease of latency, positive an increase. Star represents a statistically significant difference between blue and green light conditions ($p = 0.033$).

Secondly, we analyzed the ERP P300 amplitude recorded over all EEG electrode sites and ERP measurements. At each EEG electrode site (Fz, Cz, Pz), the normalized P300 amplitude was averaged over all participants for each light condition. Unfortunately, 3x3 (3 light conditions x 3 timepoints) repeated-measures ANOVA on normalized P300 amplitude at each EEG electrode site failed to yield statistically significant results both for the absolute amplitude values (Fz – $F(2,99) = 0.361$, $p = 0.939$; Cz – $F(2,99) = 0.461$, $p = 0.881$; Pz – $F(2,99)$

= 0.468, p = 0.876) and the differences between the control measurement in the dark and under light exposure (Fz – F(2,99) = 0.363, p = 0.937; Cz – F(2,99) = 0.294, p = 0.966; Pz – F(2,99) = 0.459, p = 0.882).

Lastly, we calculated the mean AUC of P300 response (for Fz, Pz, and Cz electrodes) in all three light conditions during three different timepoints with 5 minutes in between oddball task administration as compared to AUC under control dark condition (Figure 12). A 4x3 repeated measures ANOVA shows a significant main effect of ERP condition (F(3,130) = 4.951, p = 0.003, Cohen's f^2 = 0.013), differences between 3 light conditions, however, failed to reach a statistical significance (p > 0.05).

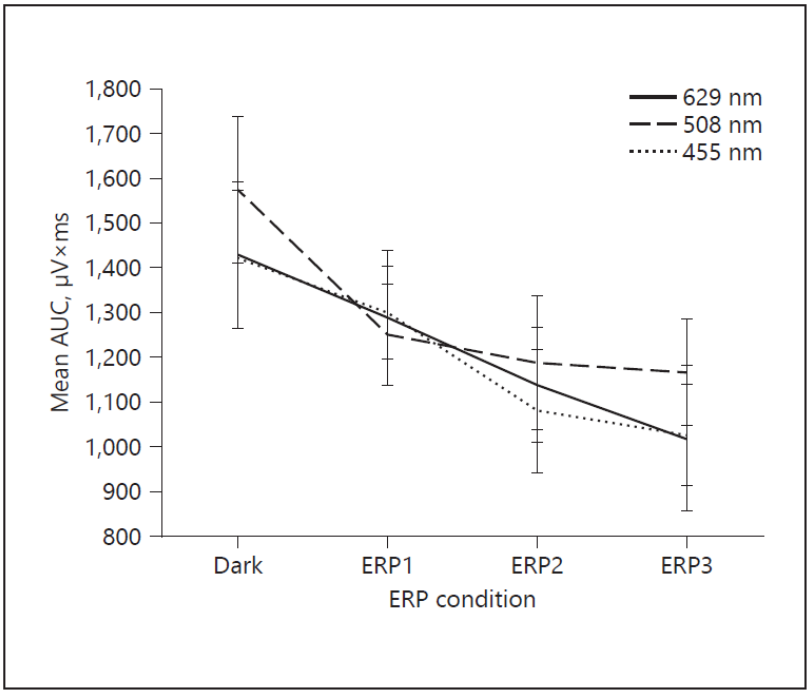

Fig 12. The mean of the AUC of P300 response in 250-500ms interval. Shown as the difference between the dark condition and measurement after light exposure of different colors. The higher the value, the smaller is the decrease of area under the P300 curve after light exposure. ERP1-ERP3 represent three timepoints of oddball task administration.

eLORETA: For eLORETA analysis, we computed the difference of normalized absolute current density power between EEG during cognitive load (PVT) in the dark condition and all three experimental light conditions. No significant differences were observed.

6.5 Discussion

In summary, the results of our study show that short-wavelength (blue) light is capable of promoting vigilance in a group of healthy volunteers during the post-lunch period. Its alertness-enhancing properties have been confirmed in both subjective and objective

measures: a decrease in one's subjective feeling of sleepiness, shorter latency of P300 response, and increased power spectral density in higher beta and gamma bands. As there is plenty of evidence showing different behavioral outcomes under light sources of polychromatic spectra (for a recent review see (Souman et al., 2018)), in the discussion, we decided to focus mainly on those few that used monochromatic sources. We show that healthy volunteers perceive their level of sleepiness differently under different light conditions, with blue light (455nm) having the strongest effect in terms of suppressing the subjective feeling of sleepiness during prolonged cognitive load as compared to green (508nm) or red (629nm) light. Our results correspond with other studies demonstrating alerting effect of shorter-wavelength blue or blue-enriched polychromatic light on human alertness using the KSS or similar instruments during morning or evening exposure (Leichtfried et al., 2015; Munch et al., 2011) and point toward a possibility of countering the decrease in alertness during the post-lunch period, in contrast with another study (Slama et al., 2015), where the authors failed to show effects of LED-equipped glasses on subjective alertness during the same time period. There are a few studies not supporting our findings in terms of the impact of short-wavelength light on subjective measures of alertness. We suspect the discrepancy is due to either lower intensity of light exposure (Okamoto & Nakagawa, 2015; Segal, Sletten, Flynn-Evans, Lockley, & Rajaratnam, 2016; Vandewalle, Maquet, et al., 2009), using polychromatic light instead of monochromatic (Santhi et al., 2013; van de Werken, Gimenez, de Vries, Beersma, & Gordijn, 2013) or different methodological approaches (Sahin & Figueiro, 2013) that may have been not as cognitively demanding as our experiment to reach a certain level of sleepiness.

As for PVT, analyses failed to show statistical significance. Qualitatively, we were able to observe a decrease of RTs under green (508nm) but not blue (455nm) or red (629nm) light, which would be in line with previous studies that also did not show a direct effect of short-wavelength light on visual (Figueiro, Bierman, Plitnick, & Rea, 2009; Slama et al., 2015) or auditory (Rodriguez-Morilla et al., 2017; Segal et al., 2016) psychomotor vigilance. However, some studies managed to demonstrate an alerting effect of shorter wavelength narrow-bandwidth light on reaction time (Beaven & Ekstrom, 2013; Lockley et al., 2006; Phipps-Nelson et al., 2009; Rahman et al., 2014), also in blind individuals with preserved light-induced melatonin suppression response (Vandewalle et al., 2013). We suspect this was due to the fact that despite the same irradiance density (14μW/cm^2) for all light conditions, the levels of illuminance differed, with green light being slightly more intensive (15.42 lux) than blue light (11.81 lux).

The results of power spectrum analysis show an increase of power density under several electrodes, mostly in higher beta (F4, Fz, T3, T4) and gamma bands (Afz, C3, C4, F3, F7, Fz, O1, T3, T4, T5, T6) in light compared to dark condition during cognitive load (PVT). Given that this increase was according to post-hoc tests observed only for the light of the shortest wavelengths (as compared to the light of middle- and long-wavelengths), we can assume that shorter wavelength light is capable of increasing EEG activity in higher frequency bands often associated with higher cognitive functioning. Unfortunately, there are only a few studies that analyzed power spectra after or during monochromatic light exposure, with inconsistent results. A study by Münch et al. (Munch et al., 2011) showed significantly higher EEG power density in some frequency bins in the alpha and beta ranges, while using polychromatic/fluorescent lightning in their protocol. Another study (Sahin & Figueiro, 2013) showed that EEG power in the alpha, alpha-theta, and theta ranges was significantly lower after exposure to red light than after the participants remained in darkness. Exposure to shorter-wavelength light reduced alpha and alpha-theta power compared to darkness, but these differences failed to reach statistical significance. In another study (Figueiro et al., 2009), exposure to red and blue light resulted in increased beta and reduced alpha EEG power relative to preceding dark conditions. Exposure to blue-enriched light during the post-lunch dip period was also found to significantly reduce the EEG alpha activity, and increased task performance (Baek & Min, 2015).

Only two studies so far used ERP P300 as a measure of cognitive brain activity. An et al. (An et al., 2009) found that 458 nm light exposure caused a significantly larger P300 amplitude that occurred with 550 nm light, with a larger P300 amplitude at nighttime than in the daytime. A larger P300 amplitude was also found in another study (Okamoto & Nakagawa, 2015) with a similar length of exposure, suggesting that the amount of attentional resources allocated to the oddball task was increased by daytime exposure to short-wavelength light. In our study, there was no significant difference in P300 amplitude or AUC; however, we found a difference in latency of P300 response. Not only was there a significant difference between the latency under blue and green light exposure, but shorter-wavelength light was also the only condition under which the latency actually decreased, which can be translated into a faster reaction time in the oddball task.

Lastly, our goal was to assess the localization of the differences in electrical activity between three light conditions using eLORETA. To our knowledge, this was the first study to have attempted to use eLORETA to demonstrate the changes in brain activity during ex-

posure to lights of different wavelengths. Unfortunately, our analyses did not detect significant differences between light conditions in terms of the localization of neural activity. In contrast, a study by Münch et al. (Munch et al., 2014) found significantly higher current densities (using HD-EEG to determine brain sources underlying the ERPs) for green and blue light after dark light adaptation (as compared to our red light adaptation) in the left middle, superior and inferior frontal gyrus, cingulate gyri, left insula and left anterior lobe of the cerebellum. Another fMRI study (Chellappa et al., 2014) showed increased light impact on executive responses in widespread prefrontal areas and the pulvinar after the participants had been exposed to longer (red) wavelength light, providing evidence that EEG responses depend on adaptation to the light of different colors as well as the color of light exposure itself and may influence the final performance in cognitive testing.

6.6 Conclusions and limitations

In this experiment, we provided further evidence that narrow-bandwidth short-wavelength (blue) light is capable of improving both subjective perception of one's levels of sleepiness and also to boost cortical activity related to cognitive tasks as measured by EEG power spectra and ERP P300 parameters. We confirmed our hypotheses, except for the reaction time as measured by PVT and current density measured by eLORETA. The limitations of our study lie mainly in our small sample and the unequal number of male and female subjects. Furthermore, we only studied the effects of light during the post-lunch period and did not take time-of-the-day differences into account, as well as the levels of light exposure during the time before the experiment. The results of the EEG measurements reflect mainly the neurophysiological responsiveness to a continuous cognitive load after a period, and therefore we cannot make any assumptions about the immediate effects of light on early EEG responses. Nevertheless, our study adds value to the research topic of acute alerting effects of light on subjective and objective measures of alertness, employing a design with monochromatic light and direct measures of cognitive performance and cortical activation. These results suggest that exposure to short-wavelength light during the day may enhance cognitive performance in task-specific scenarios, with a possible contribution to future studies and potential applications in lighting or light-filtering technology.

For further information and a detailed description of the methods used, see the original paper - (Smotek, Vlcek, Saifutdinova, & Koprivova, 2019).

7 Study 2 - Use of blue-light blocking glasses as an adjunct to cognitive-behavioral group psychotherapy for patients with insomnia

7.1 Study protocol

Patients went through a standard CBT-I group therapy program. During the first CBT-I session, participants were asked to fill in the questionnaires and received actigraphs. The first week served as a baseline measurement as the first interventions were conducted at week 2. In the second session, patients were given either active blue-light blocking glasses (BB glasses) or placebo glasses. Patients in one group had the same type. They were told that the study is focused on several types of glasses with different filtration properties. The instruction was to wear the glasses every day of the treatment at least 90 minutes before bedtime.

7.2 Participants

Forty-five patients diagnosed with insomnia were recruited at the Department of Sleep Medicine of the National Institute of Mental Health, Czech Republic, and enrolled in the CBT-I group program. Ethical approval was obtained from the local Ethical Committee. Insomnia diagnosis was established on the International Classification of Diseases, 10th edition (APA, 2013). Inclusion criteria were: a) minimum age of 18 years; b) absence of severe comorbid psychiatric, neurological or somatic disease; c) motivation to complete CBT-I program; d) stable usage of medication affecting sleep. Exclusion criteria were: a) interrupted CBT-I program; b) previous experience with CBT-I; c) night shifts. Thirty patients altogether (15 in each group) finished the study.

7.3 Methods

Subjective sleep measures: All patients were asked to complete a sleep diary every day during the therapy. The sleep logs included reports of daily lights-out time, waking and rising times, subjective estimates of sleep latency, the number of nocturnal awakenings and wake after sleep onset. There were also items recording sleep medication, ratings of sleep quality, and daytime tiredness. The diary was analyzed weekly by the leading therapist.

Patients also completed a battery of self-reported questionnaires to assess sleep complaints and daytime symptoms at the beginning and the end of CBT-I. The battery included the following questionnaires.

- ***The Pittsburgh Sleep Quality Index (PSQI):*** The Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) was used to assess sleep habits and sleep quality in the preceding two weeks.
- ***Insomnia Severity Index (ISI):*** Insomnia Severity Index (ISI) (Bastien, Vallieres, & Morin, 2001) is a 7-item questionnaire measuring the patients´ perception of their insomnia, with scores ranging from 0 (no insomnia) to 28 (severe insomnia), with 8 as a cut-off.
- ***Sheehan Disability Scale (SDS):*** Sheehan Disability Scale (SDS) (Sheehan, Harnett-Sheehan, & Raj, 1996) was used to measure daytime functioning impairment. This scale uses visual-spatial, numeric, and verbal descriptive anchors to assess disability across three domains: work, social life, and family life.
- ***Epworth Sleepiness Scale (ESS):*** To measure daytime sleepiness, the Epworth Sleepiness Scale (ESS) was administered (Johns, 1991). It is a self-administered questionnaire, where patients are asked to rate how likely they would fall asleep in presented situations in recent times on a scale ranging from 0 to 3 with a maximum total score of 24 and a recommended cut-off of 11 points.
- ***Beck Depression Inventory-2 (BDI-II):*** Beck Depression Inventory-2 (BDI-II) is a diagnostic tool measuring the symptoms of depression and their severity (A. T. Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).
- ***Beck Anxiety Inventory (BAI):*** Beck Anxiety Inventory (BAI) (Aaron T. Beck & Steer, 1993) is a self-administered questionnaire measuring actual symptoms of anxiety.
- ***Hyperarousal Scale (HAS):*** Hyperarousal Scale (HAS), a 26-item empirically designed to measure daytime alertness reflecting the enhanced arousal (i.e., hyperarousal) often found in insomnia patients was also used in the present study to assess daytime insomnia-related symptoms (Regestein, Dambrosia, Hallett, Murawski, & Paine, 1993).

Actigraphy: Patients received the devices (MotionWatch8, CamNTech, Cambridge, UK, www.camntech.com) at the beginning of CBT-I and were asked to press the event marker every time they went in or out of bed. Participants wore actigraphs on their non-dominant wrist. Data were recorded continuously for 6 consecutive weeks before they were downloaded and analyzed by a researcher blinded to the experimental condition using MotionWare 1.4 software (CamNtech).

Interventions

CBT-I: The group CBT-I program was led by two trained psychologists. The length of the program was 6 weeks, with one two-hour session per week. One group consisted of 5 to 8 patients and one therapist. Each session had a specific structure according to the recommendations of the clinical manual for insomnia treatment (Charles M. Morin & Espie, 2003). In the second week of the treatment, the sleep restriction was set up. Sleep restriction is one of the leading behavioral strategies used in CBT-I, aiming to reduce patients´ time spent in bed. Patients were recommended to spend the same amount of time in bed, as was their average TST during the previous week. The minimum length of TST was set up at 5 hours. This sleep window was titrated every week based on the following rule: if the sleep efficiency was higher than 85 %, the time in bed was prolonged by 15 minutes. Otherwise, time remained the same for another week.

Blue-light blocking glasses: For the active condition, the UVEX S1933X (U.S. certification ANSI Z87+ and CSA Z94.3) orange glasses were given to patients. Based on the used spectrum control technology, they were supposed to reduce up to 98 % of lights of blue wavelength. As the placebo condition, the UVEX S1900 (U.S. certification ANSI Z87+ and CSA Z94.3) clear glasses with no ability to filtrate blue light were used (Fig 13). Patients of both groups were instructed to wear the glasses 90 minutes before scheduled bedtime from week 2 till the end of the program. A separate item was added to the sleep diary for the patients to report the usage of glasses every evening to enhance their compliance. No adverse effects were reported by the patients.

Statistical analyses: Firstly, independent-samples t-tests were used to compare both groups at baseline. Next, a General Linear Model (GLM) was used to compare differential values (of pre- to post-treatment change) between both studied groups with age, gender, and leading therapist set as covariates. Lastly, paired t-tests were used to assess changes for each variable separately within each group. IBM SPSS Statistics software (v 23.0) was used for analyses.

Fig 13. Glasses used in the patient trial

7.4 Results

Pre- to post-treatment differences between groups: Differential values for questionnaire scores (pre- minus post-treatment value) were calculated, reflecting the change in scores reached after finishing CBT-I groups (as compared to baseline). Differences for both groups were then compared (using a GLM), finding a statistically significant difference in BAI score [$F(1, 22) = 6.389$, $p = 0.019$, Cohen's $d = 1.26$], with a larger decline in anxiety score in the active group (6.73±4.15) as compared to the placebo group (5.91±4.32). Differences in all other questionnaire scores were found to be insignificant and can be found in Table 2.

Following analyses of questionnaire scores, a comparison of the differential values of both objective and subjective sleep parameters in active and placebo groups was carried out. A statistically significant difference was found for subjective total sleep time [$F(1, 22) = 8.565$, $p = 0.008$, Cohen's $d = 0.91$], resulting in approximately 44 minutes longer TST in the active group as compared to the placebo group. Differences in all other sleep parameters were found to be insignificant and are shown in Table 3.

Effect of intervention in each group: The change between pre- and post-treatment scores for each group separately was assessed using paired-sampled t-tests. The results are to be found in Table 4. For both active and placebo groups, a significant difference was found for the following questionnaires: ISI, PSQI and SDS, and sleep parameters: subjective WASO and subjective sleep efficiency. All these results converge to show the positive effect of both conditions on sleep quality.

	N (Active/Placebo)	Active	Placebo	F	Sig.	Effect size
ISI	15/12	6.73 ± 4.15	5.91 ± 4.32	0.048	0.828	0.19
PSQI	15/12	4.20 ± 3.89	4.17 ± 2.89	0.258	0.617	0.01
ESS	14/12	0.57 ± 3.46	0.08 ± 2.50	1.443	0.243	0.16
SDS	15/12	8.77 ± 9.60	6.17 ± 8.80	0.073	0.789	0.28
HAS	15/12	4.66 ± 6.23	3.42 ± 9.38	0.020	0.889	0.16
BDI	15/12	5.93 ± 6.27	2.00 ± 4.65	1.694	0.207	0.71
BAI	15/12	4.33 ± 4.57	−0.91 ± 3.67	6.389	**0.019**	**1.26**

Table 2. Comparison of questionnaire differential values between Active and Placebo group. Mean (±SD) of difference in questionnaire scores pre- and post-CBT-I group program in groups of patients with "active" filtering glasses and "placebo" glasses. F values, statistical significance, and effect sizes (Cohen's d) are provided. Positive values indicate a decrease in scores post-treatment. ISI = Insomnia Severity Index, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, SDS = Sheehan Disability Scale, QOL = Quality of Life, HAS = Hyperarousal Scale, BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory

	N (Active/Placebo)	Active	Placebo	F	Sig.	Effect size
SOL Subj. (min.)	13/14	18.39 ± 25.05	34.30 ± 61.67	1.444	0.242	0.33
SOL Obj. (min.)	15/13	3.63 ± 8.43	5.81 ± 12.34	0.968	0.335	0.21
TST Subj. (min.)	13/14	−36.88 ± 48.68	7.04 ± 47.50	8.565	**0.008**	**0.91**
TST Obj. (min.)	15/13	9.75 ± 37.32	26.66 ± 37.24	0.024	0.878	0.45
WASO Subj. (min.)	13/14	23.32 ± 38.46	12.94 ± 20.44	0.675	0.420	0.33
WASO Obj. (min.)	15/13	6.45 ± 25.21	9.99 ± 22.76	0.066	0.800	0.15
SE Subj. (%)	13/14	−15.49 ± 12.83	−10.43 ± 10.26	3.535	0.073	0.44
SE Obj. (%)	15/13	−1.21 ± 3.94	−1.27 ± 3.06	0.066	0.800	0.02
Subj. sleep quality	13/14	−0.38 ± 1.07	−0.82 ± 1.14	0.281	0.601	0.40
Morning alertness	13/14	−0.18 ± 0.80	−0.49 ± 1.12	0.015	0.905	0.32

Table 3. Comparison of differential values of sleep parameters between Active/Placebo group. Mean (±SD) of difference in scores of objectively (actigraphy) and subjectively rated sleep parameters pre- and post-CBT-I group program in groups of patients with "active" filtering glasses and "placebo" glasses. Negative values depict an increase in the presented variables. F values, statistical significance, and effect sizes (Cohen's d) are provided. SOL = Sleep Onset Latency, TST = Total Sleep Time, WASO = Wake After Sleep Onset, SE = Sleep Effectivity.

Active (n = 15)						Placebo (n = 15)					
Sleep parameter	*Pre-treatment*	*Post-treatment*	*t*	*P-value*	*ES*	*Sleep parameter*	*Pre-treatment*	*Post-treatment*	*t*	*p Value*	*ES*
Questionnaires						Questionnaires					
ISI	17.27 ± 5.42	10.53 ± 3.36	6.29	**0.000**	**1.60**	ISI	16.83 ± 2.98	10.92 ± 3.42	4.75	**0.001**	**1.37**
PSQI	12.60 ± 4.36	8.40 ± 12.39	4.18	**0.001**	**1.08**	PSQI	13.08 ± 3.42	8.92 ± 3.20	5.00	**0.000**	**1.44**
ESS	8.71 ± 3.79	8.14 ± 4.19	0.62	0.547	0.17	ESS	5.17 ± 3.59	5.08 ± 3.53	0.12	0.910	0.03
SDS	18.97 ± 11.34	10.20 ± 6.76	3.54	**0.003**	**0.91**	SDS	14.92 ± 10.31	8.75 ± 8.11	2.43	**0.034**	**0.70**
HAS	41.60 ± 8.40	36.93 ± 10.02	2.90	**0.012**	**0.75**	HAS	35.5 ± 10.13	32.08 ± 11.28	1.26	0.233	0.36
BDI	15.13 ± 12.04	9.20 ± 9.03	3.66	**0.003**	**0.95**	BDI	11.83 ± 9.00	9.83 ± 9.38	1.49	0.164	0.43
BAI	10.80 ± 5.88	6.47 ± 4.03	3.67	**0.003**	**0.95**	BAI	10.42 ± 7.56	11.33 ± 9.99	−0.86	0.407	−0.25
Sleep diaries						Sleep diaries					
SOL (min.)	36.80 ± 27.01	18.41 ± 6.15	2.65	**0.021**	**0.73**	SOL (min.)	59.77 ± 62.30	25.48 ± 23.53	2.08	0.058	0.56
TST (min.)	369.14 ± 48.93	406.02 ± 50.16	−2.73	**0.018**	**−0.76**	TST (min.)	382.73 ± 69.27	375.69 ± 49.32	0.56	0.588	0.15
WASO (min.)	43.95 ± 41.94	20.63 ± 11.81	2.17	**0.049**	**0.61**	WASO (min.)	43.78 ± 30.64	30.83 ± 22.92	2.37	**0.034**	**0.63**
SE (%)	74.59 ± 12.63	90.09 ± 4.28	−4.35	**0.001**	**−1.21**	SE (%)	74.67 ± 11.30	85.09 ± 9.07	−3.80	**0.002**	**−1.02**
Actigraphy						Actigraphy					
SOL (min.)	12.47 ± 15.12	8.83 ± 9.83	1.67	0.117	0.43	SOL (min.)	18.12 ± 12.31	12.31 ± 11.74	1.69	0.115	0.47
TST (min.)	359.97 ± 52.18	350.22 ± 47.50	1.01	0.329	0.26	TST (min.)	378.79 ± 49.46	352.13 ± 37.17	2.58	**0.024**	**0.72**
WASO (min.)	100.78 ± 26.54	94.33 ± 29.35	0.99	0.339	0.34	WASO (min.)	112.45 ± 33.24	102.46 ± 31.60	1.58	0.140	0.44
SE (%)	74.53 ± 6.21	75.74 ± 5.67	−1.19	0.254	−0.31	SE (%)	73.68 ± 5.47	74.95 ± 5.99	−1.49	0.161	−0.41

Table 4. Effect of intervention within each group. Results of the paired-samples t-tests are presented for a group with "active" filtering glasses and "placebo" glasses. t-values, statistical significance, and effect sizes (Cohen's d) are provided. ISI = Insomnia Severity Index, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, SDS = Sheehan Disability Scale, QOL = Quality of Life, HAS = Hyperarousal Scale, BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, SOL = Sleep Onset Latency, TST = Total Sleep Time, WASO = Wake After Sleep Onset, SE = Sleep Effectivity.

Furthermore, in the active group only, a significant reduction was observed in HAS score (41.60±8.40 vs. 36.93±10.02), (t=2.90, p=0.012, Cohen's d=0.75), BDI-II score (15.13±12.04 vs. 9.20±9.03), (t=3.66, p=0.003, Cohen's d=0.95) and BAI score (10.80±5.88 vs. 6.47±4.03), (t=3.67, p=0.003, Cohen's d=0.95), while subjective TST was prolonged (369.14±48.93 min. vs. 406.02±50.16 min.), (t=-2.73, p=0.018. Cohen's d = -0.76). In the placebo group, a significant reduction of objective TST was observed (378.79±49.46 min. vs. 352.13±37.17 min.), (t=2.58, p=0.024, Cohen's d=0.72).

7.5 Discussion

The present study aimed, for the first time, to assess the effect of CBT-I in combination with BB glasses in insomnia patients. As expected, this combination was more effective in enhancing subjective sleep quality and reducing symptoms of anxiety, depression, and hyperarousal compared to CBT-I with placebo glasses. In particular, the BB glasses were associated with significantly increased subjective TST and decreased subjective SOL, unlike placebo glasses, which is in line with previous research using BB glasses in people with insomnia symptoms (Shechter et al., 2018). Moreover, BB glasses were associated with no change in objective TST, which was reduced in the group with placebo glasses. The reduction of objective TST after CBT-I has already been described in previous research as a possible consequence of sleep restriction (Kyle et al., 2014). In the present study, it seems that BB glasses helped maintain the objective sleep duration and mitigate this side effect of sleep restriction. Overall, the results are in line with studies showing a stronger impact of CBT-I on subjective sleep quality compared to objective measures (Okajima, Komada, & Inoue, 2011), further enhanced by evening blue-light filtering in the present study.

Possible interpretations related to the usage of BB glasses may lie in the interaction between the evening blue-light spectrum exposure (usually from media devices) and its effects on sleep parameters. Studies converge to show that blue-light is primarily mediated through melanopsin-based phototransduction (Bourgin & Hubbard, 2016) and exposure to it in the evening hours leads to the suppressed secretion of melatonin (Brainard et al., 2015), delayed sleep onset, decreased sleepiness and reduced slow-wave sleep activity (Gronli et al., 2016; Chang et al., 2015; Munch et al., 2011) resulting in lower subjectively perceived sleep quality. Using BB glasses in the evening may have mitigated the negative impact of evening blue-light exposure on melatonin and arousal levels, leading to better outcomes on studied sleep parameters. Increased subjective TST and decreased subjective SOL could be

associated with an earlier dim light melatonin onset (DLMO) and an improvement in circadian regulation, although this cannot be supported by objective circadian markers in the present study. This would be in line with the results of (van der Lely et al., 2015) where an attenuated LED-induced melatonin suppression in the evening and decreased vigilant attention and subjective alertness before bedtime was found after blue-light blocking glasses intervention. Similar results were also found in another study (Heo et al., 2017), where increased evening sleepiness and shorter time to reach DLMO was found in healthy adults using phones with suppressed blue-light as compared to phones with conventional blue-light emitting screens. Suppression of melatonin levels, delayed self-selected bedtime and timing of DLMO, later SOL, lower sleepiness in the evening, and lower alertness after waking up was also found in another study comparing evening usage of electronic devices and reading printed material (Chinoy, Duffy, & Czeisler, 2018). These studies further support our results of a decreased score in the hyperarousal scale in patients in the active glasses group, although this only reflects the subjective evaluation of one's hyperarousal. In contrast to the same study, where actigraphy-based sleep estimates showed no significant differences between conditions, our data show a significant change in the objective TST in the placebo group only, while the objective TST remained unchanged in the BB glasses group. All these results suggest that wearing blue-light blocking glasses in the evening may help reduce the phase-delaying effect of light and facilitate an improvement in various subjective and objective sleep parameters, making it a worthy chronotherapeutic tool to augment CBT-I with.

Interestingly, the combination of BB glasses and CBT-I was also more effective in the improvement of daytime symptoms associated with insomnia, such as depressive and anxiety symptoms. These changes were not found in a group with placebo glasses. Light and especially short-wavelength spectrum at night has been previously associated with both disrupted mood regulation (Bedrosian & Nelson, 2017) and increased cortical arousal resulting in changes in cognitive functioning (Cajochen et al., 2011; Gaggioni et al., 2014; Smotek et al., 2019). This leads to the assumption that wearing BB glasses in the evening likely ameliorates the alerting effect of light, possibly reducing the levels of cognitive arousal, as previously confirmed by (van der Lely et al., 2015). Furthermore, blocking blue light in the evening helped normalize processing speed and working memory in patients with insomnia (Zimmerman et al., 2019). To explain the differences in BAI and BDI-II scores, we also need to look into the effects of blue-light on mood regulation in various psychiatric disorders. Reduced levels of anxiety were found in a study in ADHD patients with insomnia (Fargason et al., 2013), instructed to wear blue-light-blocking glasses, where the authors also observed

a reduction of PSQI scores, fewer night awakenings, and higher morning refreshment after awakening. Another study has previously also confirmed the utility of blue-light filtration, facilitating a quicker recovery in patients in acute mania (Henriksen et al., 2016). In a study of depressed patients with sleep-onset insomnia, the authors (Esaki et al., 2017) found no significant differences in depressive symptoms or sleep quality, although half of the BB glasses group showed a clear improvement in sleep quality, suggesting that a more individualized approach may be necessary.

7.6 Conclusions and limitations

In this study, we provided the first evidence for the effectiveness of BB glasses as an augmentation of CBT for insomnia patients. As compared to wearing placebo (non-filtering) glasses, patients in the active group showed a significant increase in subjective TST, no change in objective TST, decreased hyperarousal, and lower scores in anxiety and depression measures. These results point to the fact that blue light exposure in the evening may have detrimental effects on a range of biological and behavioral functions (Green, Cohen-Zion, Haim, & Dagan, 2017). Even though recent literature review found a lack of high-quality evidence to support using blue-light blocking to improve sleep quality (Lawrenson et al., 2017), we provided new evidence that blocking blue light in the evening may provide insomnia patients with benefits beyond the effect of the behavioral therapy itself. BB glasses, therefore, seem to be a worthy, cheap, and easy-to-use, augmenting chronotherapeutic tool not only able to change subjective sleep quality, but also ameliorate mood and anxiety in patients with insomnia.

It is important to note, however, that we have not considered daytime light exposure in this study, as it may mediate or even abolish the effects of evening exposure to light (Rangtell et al., 2016). We have also not explored the potential role of chronotype nor the aspects of light hygiene before starting the CBT-I treatment. On the other hand, the effects of blocking blue light in the evening may be further strengthened by additionally increasing morning and daytime light exposure, opening new venues for the future role of chronotherapy in patients with sleep disorders. This needs to be confirmed by further studies. Another limitation of the present study lies in the low number of subjects. However, given the characteristics of this clinical sample, we think this sample represents a cohort of patients that clinicians see on a daily basis. As we think that there is enough evidence today to consider the direct effect of light on sleep characteristics, the evidence for the effects of light-blocking on anxiety and mood is currently lacking. We also think this study could greatly benefit from

studying additional objective parameters, such as melatonin serum levels or polysomnography recordings. Nevertheless, we believe these results may be of particular interest to clinicians, as it emphasizes the need to incorporate "light hygiene" (as mentioned in (Erren & Reiter, 2009) education and chronotherapeutic tools to further increase the effectiveness of CBT-I treatment.

For further information and a detailed description of the methods used, see the original paper - (Janku, Smotek, Farkova, & Koprivova, 2020).

8 Study 3 – Questionnaire survey focusing on the influence of "light-hygiene" recommendations in a healthy adult population

8.1 Study protocol

As a part of a broader questionnaire data collection, several sleep-related questionnaires were used in our study. We used Czech versions of all questionnaires, which were double-reverse translated from the originals. Permission from authors was obtained to translate and use the questionnaires.

8.2 Participants

A sample of 879 adults from the Czech Republic participated in an online survey aimed at exploring sleeping habits, chronotypes, and light hygiene. Participants were recruited via advertisement in a research center and via various social networks. Data collection was carried out between the years 2016 and 2018 using an online questionnaire platform. The selection criteria were habitual use of a mobile device during the evening or night hours and good general health according to screening questions (absence of severe health conditions and medication influencing sleep). Due to expected sleep disturbances (Krystal, 2012), we further excluded those with a history of psychiatric or severe neurological disorders (by a series of screening questions regarding present/past severe health conditions), those using psychiatric medication and people working shifts, leaving 696 participants (159 men and 538 women). Further participants were excluded due to missing data regarding length exposure, resulting in 471 participants eligible for the analysis based on light exposure before bedtime.

8.3 Methods

- **The Pittsburgh Sleep Quality Index (PSQI):** The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) was used to assess sleep habits and sleep quality in the preceding two weeks. Aside from the global score, scores from all 7 components (Subjective sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances, Use of sleeping medication, Daytime dysfunction) were analyzed independently.
- **Fatigue Severity Scale (FSS):** The Fatigue Severity Scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), is a unidimensional, nine-item self-report questionnaire scale used to measure the impact and severity of fatigue.
- **Morningness-Eveningness Questionnaire (MEQ):** Morningness-Eveningness Questionnaire (MEQ) initially developed by Horne and Östberg (Horne & Ostberg, 1976) contains 19 multiple choice questions asking for individual preferred time for different activities. MEQ score range from 16 to 86, with lower values corresponding to evening type end of the chronotype spectrum and higher values representing those with a tendency towards morningness. Several items were also analyzed independently: alertness and tiredness 30 minutes after awakening, and the tendency to wake before the alarm clock as subjective indicators of morning sleepiness. Alertness and Tiredness have been, in previous factor analyses (Caci et al., 2005; Caci, Deschaux, Adan, & Natale, 2009), attributed to 1 factor – "morning affect", which relates to one's sleep inertia. Therefore we decided to use a sum score from these two items as a single „Sleep inertia" score in further analyses.
- **Munich Chronotype Questionnaire (MCTQ):** Another chronotype-related questionnaire that we used was the Munich Chronotype Questionnaire (MCTQ) designed by Roenneberg and his team (Roenneberg et al., 2003), mainly for its ability to quantify the rate of social jet-lag (SJL) – a discrepancy between circadian and social clocks (the difference between hours of sleep on free days and working days). Aside from SJL scores values, sleep length on workdays and free days were used as separate items in analyses, to allow for a more precise characterization of sleep on free- and working days.
- **Screen exposure:** Standardized questionnaires were complemented by custom-made questions and scales examining the length and timing of the evening exposure to electronic devices (TV, PC, tablets, and phones). Visual analog scales with time descriptors (anchors) were used to mark the precise timing of this exposure, ranging

from 4 P.M. till 4. AM (end-point defined by the participants' habitual bedtime). An example of the questions used: "*Mark exactly the times when you use the TV in the given time period".* By knowing the timing of evening exposure, we were able to determine whether or not the participant was exposed to artificial screen light 90 minutes before going to bed. Similar questions were used in previous studies (Becker & Lienesch, 2018; Bhat, Pinto-Zipp, Upadhyay, & Polos, 2018; Exelmans & Van den Bulck, 2017a; Johansson, Petrisko, & Chasens, 2016; Woods & Scott, 2016). Furthermore, the length of exposure during night awakenings was gathered by simply asking the participants to estimate the time they spend on media devices while attending to various activities (sending messages, checking the time, working, watching videos or playing games) – "*If you wake up during the night, do you look at the screen of your device?"* and *"What are the activities that you perform?"*. Due to the low number of participants that used their devices actively during their awake time at night, we decided to use only two categories based on night-time activity: time checking and "light use" that contains all the remaining options mentioned above. Additionally, we enquired about the use of various filters blocking short-wavelength light (both software and hardware) – *"Do you use any filters for blocking the blue-light spectrum of your screen?"*

Statistical analyses: General linear model was used to explore the effects of cumulative screen-time exposure on sleep characteristics. t-tests were used to determine differences between observed groups dichotomized by the use of screen 90 minutes before bedtime and by their use of blue-light filters. Aditionally, ANCOVA was used to analyze differences between groups by their nighttime use of screens (no use, time checking, and light use as defined above). Nonparametric alternative (Mann-Whitney's U test) was used where the condition for equality of variances was not met. Post hoc LSD test was used to determine differences after running multiple-comparisons tests, whereas general linear model (ANCOVA) was used to control for confounding variables (age).

8.4 Results

Firstly, we looked at evening exposure length (from 4 PM until habitual bedtime) for multiple electronic screen-based devices that we inquired for in the questionnaire. Average cumulative values can be found in Table 5.

	TV		PC		Mobile		Total	
	mean	SD	mean	SD	mean	SD	mean	SD
Screen-time (h)	1.15	1.69	3.76	2.97	3.47	3.35	8.38	5.31

Table 5. Average cumulative evening screen time. Time spent watching television, using a PC, a mobile phone, and total time of evening screen exposure (as a sum of the length of exposure to all devices).

Then, we used a general linear model to assess the effects of cumulative screen exposure on selected sleep (PSQI, sleep length, sleep latency) and sleep-related parameters (FSS, social jet-lag, sleep inertia, tendency to wake up before alarm). The results are summarized in Table 6.

As we can see, statistical differences were found for morning inertia (F=1.518, p=0.019, η^2=0.141), meaning the more exposed the participants were, the less alert and more tired they felt the next morning. More hours of exposure were also associated with prolonged sleep latency on workdays (F=1.433, p=0.038, η^2=0.135). No significant associations were found for the remaining variables.

When comparing groups based on the exposure 90 minutes before bedtime (summary in Table 7), significant differences were found for sleep inertia (F=4.455, p<0.001, Cohen's *d*=0.45*)* meaning that participants that did not expose themselves to the light of device screens felt more alert and less tired the next morning. They were also more likely to wake up before the scheduled alarm clock (Z=-2.976, p =0.003, Cohen's *d*=0.30). Furthermore, social jet-lag (as measured by MCTQ) and fatigue (as measured by FSS) were greater in the group of participants that used electronic devices before going to bed (Z=-3.902, p<0.001, Cohen's *d*=0.22 and Z=-2.157, p= 0.032, Cohen's *d*= 0.15 respectively). Although subjective sleep quality (PSQI) did not differ between these two groups, we found significant differences for the PSQI components (Table 8), in particular, components 4 (habitual sleep efficiency) and 7 (daytime dysfunction). Sleep efficiency score was higher (indicating lower %) in the non-exposure group (Z=-2.753, p=0.006, Cohen's *d*=0.28) while daytime dysfunction was worse in the pre-sleep exposure group (t=3.931, p <0.001, Cohen's *d*=0.40). All these differences remained statistically significant after controlling for age, except for the total FSS score.

	Sleep Inertia	Sleep latency-Workday	Sleep latency-Freeday	Sleep on Workdays	Sleep on Freedays	Wake Before Alarm	PSQI	FSS	SJL
F	1.518	1.433	0.776	1.047	1.186	0.948	0.723	0.947	0.909
sig.	**0.019**	**0.038**	0.854	0.394	0.197	0.572	0.912	0.573	0.644

Table 6. Effect of cumulative light exposure on sleep and sleep-related parameters. Significant results are shown in bold. PSQI – Pittsburgh Sleep Quality Index total score, FSS – Fatigue Severity Scale, SJL – Social jet-lag, Sleep on Workdays/Freedays – sleep duration

	Sleep Inertia	Sleep latency—Workday	Sleep latency—Freeday	Sleep on Workdays	Sleep on Freedays	Wake before alarm	PSQI	FSS	SJL
Differences by exposure 90 minutes before bedtime									
No (N = 130)	5.05±1.69	12.79±14.92	16.52±18.06	459.46±118.33	515.79±88.38	1.40±0.49	6.74±2.31	29.40±13.15	0.83±1.10
Yes (N = 341)	4.31±1.60	12.61±12.37	14.25±12.23	468.71±127.84	523.45±122.60	1.26±0.44	6.78±2.43	32.27±12.83	1.28±1.11
Stat. test	4.455	0.130	1.561	-0.7161	-0.650	-2.976	-0.144	-2.157	-3.902
Sig.	**<0.001**	0.896	0.119	0.474	0.516	**0.003**	0.885	**0.032**	**<0.001**
Effect size	0.45	0.01	0.15	0.08	0.07	0.30	0.02	0.22	0.15
Differences by character of night time exposure									
No screen use (N = 403)	4.64±1.66	11.38±10.58	13.57±12.81	460.47±116.36	516.36±106.02	1.31±0.46	6.49±2.34	31.49±12.93	1.09±1.11
Time checking (N = 247)	4.38±1.69	13.58±13.60	15.68±14.59	468.63±131.12	515.70±103.29	1.26±0.44	7.01±2.31	35.47±12.14	1.19±1.38
Light use (N = 46)	4.78±1.77	12.98±17.90	12.98±17.90	466.11±126.07	502.83±98.26	1.36±0.49	6.78±2.64	31.91±13.94	0.98±0.88
Stat. test	2.266	2.542	1.909	1.306	0.349	0.350	3.733	7.623	0.931
Sig.	0.104	0.079*	0.149	0.705	0.705	0.272	**0.024**	**0.001**	0.395
Effect size	0.1	0.28	0.27	0.35	0.33	0.04	0.16	0.52	0.06
Differences by use of blue-light filters									
No (N = 622)	4.57±1.71	12.07±12.38	14.08±12.86	460.70±122.60	513.70±100.78	1.31±0.46	6.73±2.32	32.99±12.92	1.13±1.20
Yes (N = 74)	4.50±1.47	13.92±11.86	16.86±16.92	489.18±117.67	528.11±131.58	1.23±0.42	6.35±2.67	32.39±12.30	0.99±1.23
Stat. test	0.334	-1.220	-1.905	3.595	-1.122	-1.320	1.321	0.384	0.912
Sig.	0.739	0.223	0.090*	0.058*	0.262	0.187	0.187	0.701	0.362
Effect size	0.04	0.15	0.18	0.23	0.12	0.18	0.15	0.05	0.11

Table 7. Summary of comparative statistics. Mean values of item scores or total scores and their SD are shown, comparing groups of participants by the presence/absence of screen exposure 90 minutes before bedtime, use of blue-light filters, and exposure to screens during night awakenings. Significant results are shown in **bold**. Stars (*) represent results where a statistical trend was observed. PSQI – Pittsburgh Sleep Quality Index, FSS – Fatigue Severity Scale, SJL – Social jet-lag.

The next analysis was focused on screen exposure on mobile devices during the night (after falling asleep). We divided the sample into three groups: no screen use during sleep (N=403), light use (N=46), and time checking (N=247). After running ANOVA, we observed significant differences for the following variables (Table 7 and 8): PSQI total score (F=3.733, p=0.024, Cohen's *d*=0.16) and components 1 – Subjective sleep quality (F=3.859, p=0.022, Cohen's *d*=0.08), 2 – Sleep latency (F=3.508, p=0.031, Cohen's *d*= 0.09), 5 – Sleep disturbances (F=3.683, p=0.026, Cohen's *d*=0.07) and 7 – Daytime dysfunction (F= 4.657, p=0.01, Cohen's *d*=0.10) and FSS scores (F=7.623, p=0.001, Cohen's *d*=0.52).

Furthermore, when analyzing sub-items of the PSQI's 5th component (Sleep disturbance), we found significant differences in the number of night awakenings (F=4.628, p=0.01 *f*=0.11), troubles falling asleep (F=3.783, p=0.023, *f*=0.09) and bad dreams (F=7.301, p=0.001, *f*=0.13). After running post-hoc (LSD) tests, we found universal results for all variables: a significant difference between those that did not expose themselves to screens during night time and those that regularly checked the time on their screens, with worse outcomes in these sub-items in those that checked the time on their screens. No differences were found between groups of time-checkers and light users or light users and those that did not use screens. All these differences remained statistically significant after controlling for age (ANCOVA), except for PSQI component 7 (daytime dysfunction).

Lastly, we analyzed the use of blue-light filters, according to an answer to a simple question: whether participants did or did not use a specific filter for filtering blue-light on their screens. Only 10.6% of the sample (N=74) reported using filters, while 622 participants did not. The most prevalent means of filtering blue light were f.lux (Windows) and Twilight (Android) software. No significant differences were observed for all sleep-related variables mentioned in the previous analyses. A statistical trend was found for the duration of sleep on workdays (489 vs. 461 minutes, t=3.595, p=0.058, Cohen's *d*=0.23), meaning those that used blue-light filters slept in average approximately 28 minutes longer on a workday than those that did not use any means of filtering blue-light (Table 7). No other differences were observed.

	PSQI #1 (Sleep Q.)	PSQI #2 (Sleep lat.)	PSQI #3 (Sleep dur.)	PSQI #4 (Sleep eff.)	PSQI #5 (Sleep dis.)	PSQI #6 (Sleep med.)	PSQI #7 (Dayt. dysf.)
Differences by exposure 90 minutes before bedtime							
No (N = 130)	0.91±0.72	0.88±0.87	0.37±0.60	1.91±1.44	1.18±0.46	0.11±0.51	1.38±0.80
Yes (N = 341)	1.01±0.74	0.90±0.83	0.41±0.67	1.49±1.50	1.19±0.48	0.07±0.30	1.70±0.79
Stat. test	1.777	0.072	0.375	7.619	0.158	1.567	15.451
Sig.	0.183	0.788	0.540	**0.006**	0.691	0.211	**<0.001**
Effect size	0.13	0.02	0.06	0.28	0.02	0.09	0.40
Differences by character of nighttime exposure							
No screen use (N = 403)	0.89±0.73	0.79±0.79	0.39±0.66	1.75±1.48	1.13±0.45	0.05±0.32	1.48±0.79
Time checking (N = 247)	1.03±0.74	0.95±0.86	0.45±0.75	1.59±1.50	1.22±0.48	0.08±0.33	1.67±0.78
Light use (N = 46)	1.11±0.77	1.00±0.84	0.35±0.56	1.37±1.51	1.26±0.49	0.04±0.21	1.65±0.82
Stat. test	3.859	3.508	0.949	1.891	3.683	1.029	4.657
Sig.	**0.022**	**0.031**	0.388	0.152	**0.026**	0.358	**0.010**
Effect size	0.08	0.09	0.04	0.09	0.07	0.23	0.10
Differences by use of blue-light filters							
No (N = 622)	0.96±0.73	0.85±0.82	0.42±0.70	1.70±1.48	1.18±0.47	0.05±0.28	1.57±0.80
Yes (N = 74)	0.95±0.82	0.93±0.86	0.28±0.56	1.42±1.51	1.09±0.44	0.16±0.52	1.51±0.80
Stat. test	0.014	0.591	2.822	2.291	2.415	8.330	0.305
Sig.	0.907	0.446	0.093	0.131	0.121	0.074	0.581
Effect size	0.01	0.09	0.22	0.18	0.20	0.26	0.08

Table 8. Summary of comparative statistics of single PSQI components. Mean values of item scores or total scores and their SD is displayed, comparing groups of participants by the presence/absence of screen exposure 90 minutes before bedtime, use of blue-light filters, and exposure to screens during night awakenings. Significant results are shown in bold. The 7 components are: Subjective sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances, Use of sleeping medication, and Daytime dysfunction.

8.5 Discussion

When employing an indirect measurement of cumulative screen exposure during evening hours, we found a significant association between screen exposure and sleep inertia, suggesting that light in the evening may not only increase cortical arousal during evening hours but can influence one's alertness the following morning, as shown by other studies as well (Green et al., 2017; Chang et al., 2015; Chinoy et al., 2018). Additionally, a moderate association was found for sleep latency on workdays, with longer latencies in those exposing themselves more to the light of media screens, which is in line with another study, where direct measurement of screen-time using a smartphone application was employed and where longer average screen-time was associated with shorter sleep and worse sleep efficiency (Christensen et al., 2016). A study by Heath et al. (Heath et al., 2014) failed to show significant differences in morning functioning between bright tablet screen and filtered screen use for 1 hour before bedtime, suggesting longer evening exposure, like in our sample, may be needed to observe differences in daytime functioning.

As the cumulative screen exposure during evening hours may seem like an arbitrary variable not directly related to sleep, we also decided to analyze the data based on whether the participants did or did not expose themselves 90 minutes before sleep. This time period seems to be most relevant for the potential effects of screen light on the suppression of melatonin, although it does not fully reflect individual DLMO (Keijzer, Smits, Duffy, & Curfs, 2014), as no direct measurement of melatonin levels was used in our study. Our results show that the exposure to artificial screen light 90 minutes before sleep is associated with increased sleep inertia in the mornings and a tendency to rely on the alarm clock to wake up in the morning. Although no differences in PSQI scores were observed, those exposed to light before sleep had significantly higher scores in PSQI's daytime dysfunction component and lower scores in the sleep efficiency component. While daytime dysfunction can be easily explained in terms of lower alertness and stronger feelings of tiredness in the morning, lower sleep efficiency in the non-exposure group is harder to interpret. Due to insignificant differences in sleep length, and the fact that sleep efficiency was only based on subjective reports included in the PSQI and not on sleep diaries or actigraphy, the most likely interpretation would be that sleep efficiency, as a sleep parameter does not fully reflect the quality of subjectively perceived sleep.

Another factor that we analyzed in relation to sleep quality was exposure to screens during night hours – whether to check new emails/messages or just to check the time. We found that frequent time-checking was associated with an increase in night awakenings,

higher prevalence of bad dreams, and higher PSQI total score (with significant differences in components 1 – subjective sleep quality, and 5 – sleep disturbances) and FSS scores. Light use of devices during night awakenings showed no effects, most likely due to the low number of participants in this group. All these results point towards worse daytime functioning and more sleep disturbances in those who expose themselves to artificial light during sleep, which was also shown by a field PSG study (Wams et al., 2017), where the authors described more awakenings during the night, shorter latency to first REM sleep and less REM sleep in those exposed to more light in the evening. In contrast, no differences were found in sleep onset latency, eye-movements, slow-wave sleep or REM sleep in the two first sleep cycles in a study by Heath et al. (Heath et al., 2014), once again suggesting that shorter (1 hour) evening exposure may not be enough to change objective sleep characteristics. Other studies (Bhat et al., 2018; Exelmans & Van den Bulck, 2017b; Thomee, Harenstam, & Hagberg, 2011; Woods & Scott, 2016) focused on the evening, and night-time media use itself, with congruent findings showing that more mobile device-based electronic media use led to higher levels of insomnia, anxiety and shorter sleep duration on weeknights (Bhat et al., 2018) and sleep disturbances (Exelmans & Van den Bulck, 2017b; Thomee et al., 2011) in adults and poorer sleep quality in adolescents (Woods & Scott, 2016). Furthermore, bad dreams, or nightmares and their association with the use of technology has been shown in previous studies (Arora, Broglia, Thomas, & Taheri, 2014; Choi et al., 2009), pointing towards the disruptive potential of pre-sleep cognitive arousal, although the precise mechanisms involved have not yet been investigated.

An interesting finding is that a relatively short time-checking at night was enough to disturb the participant's sleep as no differences were observed between those who checked the time at night and those that could be characterized as night-time related light users (texting, social media use, etc.). This may potentially reflect short-wavelength light's ability to swiftly modulate cortical arousal in brain regions associated with cognitive processing (Vandewalle, Gais, et al., 2007), rather than content-related "fear of missing out" often reported in social media studies (e.g. (Bhat et al., 2018; Kuss & Griffiths, 2017)). Also, time-checking itself may contribute to increased arousal and lead to further concerns about sleep as typically seen in people suffering from insomnia (Riemann et al., 2017).

Lastly, we found that the use of blue-light filters as a part of sleep hygiene was present only in 10.6% of our participants. The number of participants using filters suggests the need for further education of the general public, given the fact that everybody is exposed to artificial light in one way or another. A positive finding is that the average age of the group

that uses filters is lower, suggesting that not only is it the young cohort that is the most exposed to electronic devices but that they are also the most educated in terms of the adverse effects of short-wavelength light on our sleep. Unfortunately, the results from our data sample regarding light filtration were not as convincing as expected. The only relevant results (statistical trends) found were the differences in the duration of sleep on workdays and the number of night awakenings, suggesting that filter use may have positive effects on our sleep. These results make perfect sense as longer sleep latencies displace our main sleep period further into the morning, causing us to stay in bed longer. We do realize that apart from the use of filters, we have not controlled for other factors that may have contributed to unconvincing results, such as ambient room light or filter parameters. We believe that adopting a different study design, with standardized filter parameters or blue-light blocking glasses, may yield different results.

Although recent literature review found lack of high-quality evidence to support using blue-light blocking to improve sleep quality (Lawrenson et al., 2017), many studies, both of questionnaire (Polos et al., 2015; Xanidis & Brignell, 2016) and interventional designs (Ayaki et al., 2016; Heo et al., 2017; Knufinke et al., 2018; Perez Algorta et al., 2018; van der Lely et al., 2015; Zimmerman et al., 2019) show the negative association between evening screen exposure and our sleep and potential benefits of filtering this narrow-band color spectrum. A study on recreational athletes (Knufinke et al., 2018) found that using amber-lens glasses in the evening shortened subjective sleep onset latency, improved sleep quality, and increased alertness the following morning. Another study (Heo et al., 2017) found that the use of suppressed blue-light phone screen for 150 minutes in the evening resulted in increased sleepiness and shorter time to reach DLMO, which is in accord with a study of Ayaki et al. (Ayaki et al., 2016), who found that blue-light shield eyewear for media devices used for 2 hours before bedtime was effective in increasing sleep efficacy and decreasing sleep latency and increasing overnight melatonin secretion, similarly to the results of another study (van der Lely et al., 2015), that also described decreased vigilant attention and subjective alertness in the evening as a result of using blue-blocker glasses for 3 hours.

Furthermore, it is important to note that the role of chronotype (one's temporal phenotype(Roenneberg, Pilz, Zerbini, & Winnebeck, 2019)) was not considered in the present paper, as the majority of studied characteristics (fatigue, sleep inertia) reflect one's subjective perception regardless of the timing. Although the environmental light-dark cycle is a major synchronizer of circadian rhythms and that variations in exposure to bright light (both

natural and artificial) might be associated with variations in chronotype, findings from studies(Martin, Hebert, Ledoux, Gaudreault, & Laberge, 2012; Porcheret et al., 2018; Refinetti, 2019) remain inconclusive, and further research is necessary to elucidate all mechanisms in action. Another factor that has not been considered in the present study is the content watched on the screens. Personally relevant content may seem particularly important, as it can lead to high arousal positive (happiness) or negative (jealousy, anxiety) states (Bowler & Bourke, 2018), further contributing to worse sleep outcomes.

8.6 Conclusions and limitations

In the present study, we provided further evidence that evening and night-time exposure to screens of media devices may have harmful effects on subjectively perceived sleep quality and daytime functioning in a cohort of healthy individuals, with small-to-medium effect sizes. We also showed that limiting evening exposure length may be beneficial in terms of various sleep and sleep-related parameters. Unfortunately, little to no results were found for the effects of blue-light filtering. We suspect that the insignificant results were mainly due to a lower number of participants using means of filtering. Another limitation may lie in the gender imbalance, although no significant differences were observed in the present study. As people with neurological or psychiatric disorders and people working shifts have not been included in this study, it would be inappropriate to generalize our results also for these cohorts. Furthermore, we did not control specifically for other factors influencing light exposure (e.g., intensity, duration(Wood, Rea, Plitnick, & Figueiro, 2013), light spectral composition, distance from the screen, etc.) nor did we not take the levels of light exposure during the day(Rangtell et al., 2016) or ambient light during the evening/night hours into account. This is mainly a limitation of the questionnaire study design, and we believe these results may encourage future studies to adopt a different approach with more objective measures (EEG polysomnography recordings, melatonin levels) as more and more robust evidence of the negative impact of artificial light has been appearing in the scientific literature. At the same time, the implementation of blue-light blocking interventions seems like a promising and easy-to-use tool of attenuating these effects.

Despite the lack of direct light exposure-related parameters in the present study, our study design adds value to the research topic of the impact of evening/night-time artificial screen light on sleep and next-day functioning, as it considers multiple subjective sleep-related parameters and a large sample that would have been otherwise hard to reach with the application of more direct - objective measurements.

For further information and a detailed description of the methods used, see the original paper - (Smotek, Farkova, Mankova, & Koprivova, 2020).

9 CONCLUDING REMARKS AND IMPLICATIONS OF OUR RESULTS

Three studies have been carried out as a part of this dissertation. In the first study, an EEG laboratory experiment, shows that short-wavelength (blue) light is capable of promoting vigilance in a group of healthy volunteers. Its alertness-enhancing properties have been confirmed in both subjective and objective measures: a decrease in one's subjective feeling of sleepiness, shorter latency of P300 response, and increased power density in higher beta and gamma bands. In the second study, a trial on insomnia patients showed that the combination of standard cognitive-behavioral therapy program with blue-light blocking glasses was more effective in enhancing subjective sleep quality and reducing symptoms of anxiety, depression, and hyperarousal compared to CBT-I with placebo glasses. And finally, the third study, an online questionnaire survey, showed a negative association between evening and night screen exposure and our sleep and potential benefits of adhering to "light hygiene" recommendations, such as filtering blue light spectrum or avoiding screen exposure in the evening and night hours.

Altogether, our data represent a valuable contribution to current sleep and chronobiology research as they enhance understanding of the blue light's effects on human sleep and cognition, employing up-to-date unique research designs with a potential to lead to the development of new lighting or light-filtering systems and applications for healthy sleep promotion in both the general and clinical populations.

The EEG experiment provided further evidence that narrow-bandwidth short-wavelength (blue) light is capable of improving both subjective perception of one's levels of sleepiness and also to boost cortical activity related to cognitive tasks as measured by EEG power spectra and ERP P300 parameters. This shows that EEG recording and especially the use of event-related potentials, is a valid source of information when it comes to measuring neurophysiological reactions to different light sources. The limitations of this study lie mainly in the small sample size, which could have been the reason for no significant differences in current density measured by eLORETA. Nevertheless, using a design with monochromatic lights of different colors but the same irradiance density brought additional information about the biological effect of these three short/medium/long wavelength-lights and corresponds to the recent methodological recommendations of Prayag and colleagues

(Prayag, Münch, et al., 2019). This is also in line with suggestions of recent review studies, where for instance, Katsuura and Lee appeal to build a truly adapted artificial environment based on the biological characteristics of human beings (Katsuura & Lee, 2019). Similarly, Bourgin & Hubbard believe that a more detailed spectral management of lights could also be applicable to many daily living conditions, far beyond simply the workplace or the home, allowing us to also better adapt to situations like transmeridian travel or shift-work (Bourgin & Hubbard, 2016).

Our second study, a combined psychotherapeutic and chronotherapeutic (BB glasses) intervention, showed to be more effective in enhancing subjective sleep quality and reducing symptoms of anxiety, depression, and hyperarousal in insomnia patients compared to intervention with placebo glasses. This was one of the few studies that focused on a clinically-relevant sample (in addition to (Esaki et al., 2016; Esaki et al., 2017; Henriksen et al., 2016; Shechter et al., 2018; Zimmerman et al., 2019)) and the first study to have used blue-light blocking glasses in addition to a standardized psychotherapeutic intervention. Our study showed that wearing blue-light blocking glasses in the evening may help reduce the phase-delaying effect of light and facilitate an improvement in various subjective and objective sleep parameters, depressive and anxiety symptoms, and hyperarousal, alleviating most of the symptoms that insomnia patients struggle with. Application of this easy-to-use and cheap tool could lead to additional indications of light interventions as a complementary and innocuous treatment to help patients with sleep or other psychiatric symptoms, as proposed by Blume et al. (Blume et al., 2019).

Our third study showed that above-average exposure to screens of media devices was associated with sleep inertia, suggesting that light in the evening may not only increase cortical arousal during evening hours but can influence one's alertness the following morning as well. Furthermore, being exposed to media screens was associated with prolonged sleep latency on workdays, more daytime dysfunction, more night awakenings, and sleep disturbances, and higher fatigue scores. On the other hand, the use of blue-light filters was associated with increased sleep duration and fewer night awakenings. All these results point towards worse sleep and daytime functioning in those who expose themselves to artificial light in the evenings and at nights and possible benefits of blocking the blue part of the light spectrum. The main benefits of this particular study lie in the relatively high number of participants and a broad spectrum of sleep and sleep-related questionnaires used. Unlike previous studies, we have explicitly focused on the length and timing of screen exposure, which in return brought impressive results further applicable for healthy sleep promotion, not only

in a healthy population but in patient populations as well. Although recent literature review found a lack of high-quality evidence to support using blue-light blocking to improve sleep quality (Lawrenson et al., 2017), two of our studies clearly show the benefits of blocking or avoiding artificial light in the evening and night hours. The effects of the absence of artificial light exceeded mere improvements in sleep. Enhancement of daytime functioning and decline in depressive and anxiety symptoms has been shown. Incorporating recommendations regarding appropriate light exposure into the practices of sleep hygiene may, therefore, help to promote public health and prevent disease, as initially proposed by Erren & Reiter (Erren & Reiter, 2009).

Furthermore, these results also add to the potential of creating „circadian-friendly" lighting systems, incorporating suggestions from recent studies (Canazei et al., 2019; Okkels et al., 2020; Scott et al., 2019) or newly-studied metamere light (Allen et al., 2018; de Zeeuw et al., 2019) to promote new designs of lighting systems that do not lead to chronodisruption. Several limitations of studies for this thesis have already been mentioned and mainly include small sample sizes and limited ability to control for all possible confounding variables. These are also the recommendations from a recent review (Tahkamo et al., 2019) that calls for repeated measure designs, and also, systematic reviews on other light-induced health concerns, as well as meta-analyses of any adverse health impacts, to further clarify the scientific evidence on impacts of light on human health. Also, other factors that influence the effects of light should be considered, such as chronotype, circadian phase, homeostatic state, prior light history, and genetic disposition, as they may obscure its effects on sleep and cognition. Recently, suggestions have also been made to validly measure and compare the biological effects of light and light filters, and novel physiologically relevant and retinally referenced frameworks for quantifying have been published (Prayag, Münch, et al., 2019; Spitschan et al., 2019). Future studies should, therefore, keep better track of these factors and take them into account when evaluating the effects of light exposure (Souman et al., 2018).

Tables overview

Figures overview

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Appendix – Publications of the graduant

Original papers related to this dissertation:

In English:

Šmotek, M., Vlček, P., Saifutdinova, E., & Kopřivová, J. (2019). Objective and Subjective Characteristics of Vigilance under Different Narrow-Bandwidth Light Conditions: Do Shorter Wavelengths Have an Alertness-Enhancing Effect?. ***Neuropsychobiology***, *78*(4), 238–248. https://doi.org/10.1159/000502962 **(IF 1.675)**

Janků, K., **Šmotek, M.**, Fárková, E., & Kopřivová, J. (2020). Block the light and sleep well: Evening blue light filtration as a part of cognitive-behavioral therapy for insomnia. ***Chronobiology international***, *37*(2), 248–259. https://doi.org/10.1080/07420528.2019.1692859 **(IF 2.562)**

Šmotek, M., Fárková, E., Manková, D., & Kopřivová, J. (2020). Evening and night exposure to screens of media devices and its association with subjectively perceived sleep: Should "light hygiene" be given more attention?. ***Sleep health***, S2352-7218(19)30258-X. In press, corrected proof. Advance online publication. https://doi.org/10.1016/j.sleh.2019.11.007 **(SJR 1.424)**

In Czech:

Šmotek, M., Kopřivová, J., Šóš, P. (2016). [Blue light and its effects on circadian system, sleep and cognitive performance]. ***Psychiatrie***., 20(1), 29-34.

Other publications:

Janků, K., **Šmotek, M.**, Fárková, E., & Kopřivová, J. (2020). Subjective-objective sleep discrepancy in patients with insomnia during and after cognitive behavioural therapy: An actigraphy study. ***Journal of sleep research***, e13064. Advance online publication. https://doi.org/10.1111/jsr.13064 **(IF 3.432)**

Fárková, E., **Šmotek, M.**, Bendová, Z., Manková, D., & Kopřivová, J. (2019). Chronotype and social jet-lag in relation to body weight, apetite, sleep quality and fatigue. ***Biological Rhythm Research***, https://doi.org/10.1080/09291016.2019.1630096 **(IF 0.773)**

Fárková, E., Schneider, J., **Šmotek, M.**, Bakštein, E., Herlesová, J., Kopřivová, J., Šrámková, P., Pichlerová, D., & Fried, M. (2019). Weight loss in conservative treatment of obesity in women is associated with physical activity and circadian phenotype: a longitudinal observational study. ***BioPsychoSocial medicine***, *13*, 24. https://doi.org/10.1186/s13030-019-0163-2 **(IF 1.197)**

Book chapters:

Janečková, D., Weissová, K., Fárková, E., Veldová, K., Lišková, M., Dudysová, D., **Šmotek**, M., Kopřivová, J., Bendová, Z. Ranní ptáče dál doskáče... Ale co sovy?. In: Horáček, J., Kesner, L., Höschl, C., Španiel, F. ***Mozek a jeho člověk, mysl a její nemoc***. Praha: Galén, 2016, s. 146-152. ISBN: 978-80-7492-283-1.

Conference abstracts:

Janků, K., **Šmotek, M.**, Fárková, E., Miletínová, E., Kopřivová, J. Blue light blocking glasses and CBT-I: effect on subjective and objective sleep quality, ***Sleep Medicine***, Volume 64, Supplement 1, 2019, Page S174, ISSN 1389-9457

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