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# CLINICAL REVIEW Revisiting the alerting effect of light: A systematic review

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# SUMMARY

Light plays an essential role in maintaining alertness levels. Like other non-image-forming responses, the alerting effect of light is influenced by its spectral wavelength, duration and intensity. Alertness levels are also dependent on circadian rhythm (process C) and homeostatic sleep pressure (process S), consistent with the classic two-process model of sleep regulation. Over the last decade, there has been increasing recognition of an additional process (referred to as the third process) in sleep regulation. This third process seems to receive sensory inputs from body systems such as digestion, and is usually synchronised with process C and process S. Previous studies on the alerting effect of light have been mostly conducted in laboratories. Although these studies are helpful in delineating the impact of process C and process S, their ability to assist in understanding the third process is limited. This systematic review investigated the factors that influence the alerting effect of light by examining randomised controlled trials and randomised or counterbalanced crossover studies. Factors that influence light's alerting effect was examined separately due to its potential to offer flexible workplace-based light interventions to increase or maintain employees' alertness.

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# Introduction

As one of the most powerful environmental stimuli, light's impact on humans extends beyond its classic visual function to other brain functions. These other brain functions are referred to as non-image-forming (NIF) responses to separate them from the classic visual responses to light. Examples of NIF responses include circadian rhythm phase shifting [1,2], pupillary reflexes [3], mood changes [4], acute melatonin suppression [5,6], improved cognitive function [7,8] and the promotion of alertness levels [7,9,10]. Over the last decade [7,11,12], there has been growing interest in understanding the neurophysiological pathways via which light influences alertness levels, partly due to its potential to be applied in real world settings as a countermeasure for sleepiness.

Central to the physiology of light's NIF responses, including light's alerting effect, are the intrinsically photosensitive retinal ganglion cells (ipRGC) located in the retina. Although these ipRGCs only account for 1–5% of the total ganglion cells [13], their role in light's NIF responses is fundamental and is independent of the

classic visual system. For example, in completely blind participants, light is able to modulate electroencephalogram (EEG) activity and impact the subcortical areas that regulate alertness levels when participants are engaged in cognitive tasks [14]. ipRGCs primarily receive input from melanopsin, an ipRGC expressed photoreceptor [15], but also receive input from rod-cone networks [13]. Rods and cones are most sensitive to medium and long wavelength light, whereas melanopsin photoreceptors have a maximum sensitivity to short wavelength light of 480 nm (blue light) [13]. Predictably, blue light has been found to have a greater influence on the thalamus and the frontal and parietal cortical areas than green and violet light [8,16]. In addition to wavelength, the alerting effect of light is also associated with the duration and intensity of light exposure. For instance, a dose-response relationship between light intensity and its alerting effect has been observed during biological night (23:00–07:00 h for normal chronotypes) [17]. Furthermore, a longer duration of white intense light is predictive of larger brain activation [18]. Collectively, previous studies have clearly demonstrated the importance of light's physical properties in promoting alertness levels; however, light's alerting effect must also be considered within a broad sleep regulation framework.

The earliest and most tested model of sleep regulation is the two-process model, which comprises two separate processes [19].





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Abbreviations	
EEG	electroencephalogram
ipRGC	intrinsically photosensitive retinal ganglion cells
KSS	Karolinska sleepiness scale
KGS	Kwansei Gakuin sleepiness scale
MSLT	multiple sleep latency test
MWT	maintenance of wakefulness test
NIF	non-image-forming
PSG	polysomnography
RCT	randomised controlled trial
SCN	suprachiasmatic nucleus
SEM	slow eye movements
SSS	Stanford sleepiness scale
VAS	visual analogue scale

process C, representing the circadian rhythm, is usually high during the day to facilitate activity and low during biological night to facilitate sleep. process S, representing sleep debt, increases during wakefulness and decreases during sleep. In this original model, these two processes interact only at discrete time points. The authors of the two-process model acknowledge that this model does not incorporate some of the complexities that have been discovered since its conception [19]. One complexity is the continuous and non-linear interaction between process C and process S, which allows immediate reciprocal feedback between these two processes. The other complexity is the non-suprachiasmatic nucleus (SCN) oscillator that is linked to metabolic rate, which is further influenced by factors such as food intake and energy consumption. This non-SCN oscillator is usually synchronised with the central SCN clock, but can be desynchronised under certain conditions [19]. This continuous interaction between process C and process S was also recognised by another group of researchers led by Hubbard [11], who postulated a three-process conceptual framework of sleep regulation – that is, process C, process S and a direct effect – following their review of studies on transgenic mice. The direct effect in Hubbard et al.'s model refers to the direct effect of light on sleep that is independent of, but interacts with, circadian rhythm. The idea of an additional process to process C and S in regulating sleep was also proposed by Johns [20], who developed a similar conceptual framework. In Johns' framework, this additional process is expressed as process A, which works with process C and process S in regulating sleepiness. process A represents an afferent process, integrating sensory inputs from body systems e.g., postural muscles [20]. Although different terms have been used by the above mentioned researchers, namely Borbely and his associates, Hubbard and his team, and Johns, all of them suggest a new and independent process to process C and process S in regulating sleep. This new process seems to encompass a range of endogenous (e.g., chronotype) and exogenous (e.g., physical activity, food intake) factors that are often eliminated or controlled in laboratory studies for the purpose of disentangling the role of process C and process S in sleep regulation. However, to enable the application of light intervention as a sleepiness countermeasure in the real world, understanding how this third process impacts light's alerting effect is vital.

The purpose of this review is to describe light intervention studies in reference to the three-process conceptual framework and considering the physical properties of light. While previous reviews aimed to clarify the underlying neurophysiological pathways via which light affects alertness levels, this current review aims to broadly document factors that influence the alerting effect of light in their most complete form, and search for patterns amongst both effective and non-effective light interventions. The results of this review will be briefly discussed in relation to the underlying physiological mechanisms as well as the methodological quality of the studies. The findings are particularly relevant to industries where alertness levels are crucial to the safety of clients, such as health care professionals and rail workers [21,22], where poor decision-making has major consequences (e.g., death).

# Methods

# Eligibility criteria

#### Study design

Eligible studies were restricted to randomised controlled trials (RCT) and randomised or counterbalanced crossover studies. A counterbalanced crossover design was considered appropriate for testing the alerting effect of light, because the alerting effect of light is short-lived [23] and in people without significant sleep disorders, levels of alertness are generally stable. This criterion requires studies to explicitly state that participants were randomly allocated to different treatment conditions, or to order of treatment, or to state that the order of treatment was counterbalanced. To this end, studies using methods of non-random allocation to treatment (e.g., by participants' office floor [24]) were excluded. Studies that failed to report the method for allocation to treatment were excluded without contacting authors for further details.

#### Study participants

Adults without medical conditions known to influence their alertness levels were included. Healthy employees or volunteers were both considered eligible. On the other hand, studies examining 1) people aged 55 y and above, or 2) a clinical population, such as patients with a diagnosis of Parkinson's disease, depression, brain injury or dementia were excluded. Older people were excluded because there is evidence that the regulation of circadian rhythm weakens as people age [25], which might result in an attenuated alerting response to light intervention.

#### Types of interventions

Studies using light alone or with other interventions were selected. To enable the elucidation of the impact of intensity and spectral wavelength on the alerting effect of light, studies were required to report both aspects across treatment conditions to allow the differences in spectral distribution and illuminance level between intervention and controls to be determined. Light source (e.g., fluorescent, incandescent, daylight) was used as a proxy of spectral power distribution when the spectral power distribution or correlated colour temperature was not available. On the other hand, studies that failed to report intensity and/or spectral distribution for any treatment conditions were excluded. For studies that used light and other forms of intervention (e.g., fixed sleep schedule), these studies were only included when light's alerting effect could be ascertained.

#### *Outcome measures*

The outcome of interest for this review was alertness/sleepiness. Both subjective and objective alertness measurements were considered. Validated instruments for the measurement of subjective alertness included the Karolinska sleepiness scale (KSS) [26], Stanford sleepiness scale (SSS) [27], visual analogue scales (VAS) and other self-reported scales such as the Kwansei Gakuin sleepiness scale (KGS) [28].

Objective measures of alertness/sleepiness comprised EEG correlates which included alpha (8-12 Hz), theta (4-8 Hz) and delta

power density (1–4 Hz). Increased homeostatic sleep pressure has been found to result in increased frontal low EEG (theta/delta; 1–7 Hz) activity [29]. Moreover, subjectively measured sleepiness has been found to be negatively associated with global alpha power density and positively associated with frontal theta power density (4–8 Hz) [30]. Incidences of slow eye movements (SEMs) that occur before sleep onset are highly correlated with subjective sleepiness and EEG low frequency activity, although this relationship is almost exclusive to an eye closed condition [31] among sleep deprived participants. Also, the maintenance of wakefulness test (MWT) [32] and multiple sleep latency test (MSLT) were considered in this review. Behavioural alertness/sleepiness measures, such as cognitive performance tests were excluded as they vary in task difficulty, which is a factor that influences alertness [33].

## Electronic databases

PubMed, EMBASE, PsycINFO and Scopus databases were searched until December 2016. A list of keywords and keyword combinations used is provided in Appendix 1.

# Study selection

Study selection was completed using a three-step process. At Step 1, the titles and abstracts of returned citations were read by both authors. Studies that were clearly irrelevant to the topic or did not meet inclusion criteria were excluded. At Step 2, inspection of the full texts of the remaining studies was conducted by the two authors regarding their eligibility. At Step 3, key information from the remaining articles was extracted independently by the two authors, resulting in some studies being further excluded.

#### Data extraction

Data on study design, sample, light treatment profile and alerting effect were extracted. Study sample was described in terms of 1) occupation 2) sample size, 3) average age, 4) percentage of females, and 5) eligibility criteria to participate. Light treatment profiles included the 1) intensity and spectral wavelength of the light, 2) timing of light intervention, 3) duration of a single light intervention session, 4) the number of light treatment sessions within one 24-h cycle, and 5) the number of 24-h cycles. Participants' sleep history in the 48 h prior to light intervention was examined by documenting the sleep wake schedule and length of sustained wakefulness for the two nights prior to the light intervention. Prior light exposure immediately before intervention was also assessed. Lastly, the effectiveness of light treatment in improving alertness levels during and after light exposure was documented, respectively. A meta-analysis of the effect size of the alerting effect was planned; however, it was not possible because of the limited usable data and the heterogeneity of the studies.

#### Risk of bias assessment

Risk of bias assessment was undertaken using the guidelines for intervention studies from the Cochrane's handbook [23]. For RCTs, the risk of selection bias, performance bias, detection bias, bias due to incomplete data and reporting bias were evaluated. For studies with a crossover design, the examination of possible carryover effects, the availability of a complete data set and the use of paired analysis was examined. Risk of bias was evaluated by two authors. Disagreements were resolved through discussion.

#### Results

A flowchart of the literature screening process is presented in Fig. 1. In total, 28 studies were included, with 24 studies examining the alerting effect of light during illuminance (see Table S1) and 14 investigating the post-illuminance effect (see Table S2). Of the 28 studies, 10 studies examined alertness levels both during and post-illuminance. Note, in presenting the results, the alertness level measured immediately after the completion of light intervention was classified as being during illuminance.

# *Light interventions for promoting alertness* **during** *illuminance* (N = 24)

Among the 24 studies that examined the alerting effect of light during illuminance, 11 studies were undertaken in the daytime, and 13 were conducted at night (see Table S1). Regarding study design, six of the 24 studies used a RCT design [9,10,33–36], and the remaining studies used a crossover design. Participants were all healthy volunteers, usually aged between 20 and 25 y, who underwent extensive screening before being recruited to the study. The sample size ranged from 8 [28,37,38] to 64 [39], and was generally around 10 to 20 participants.

### Daytime studies (N = 11)

Of the 11 daytime light studies, three studies [10,39,40] found a significant *during illuminance* alerting effect, six studies reported a non-significant alerting effect [33,35,37,41–43] and two studies reported mixed results regarding the alerting effect of light where light had an alerting effect on an objective but not a subjective measure [34,44]. The details of these studies are outlined below.

# Studies with significant alerting effect (N = 3)

The three studies [10,39,40] that observed a significant alerting effect all used a 1000 lux fluorescent light as the intervention. Comparison light conditions differed slightly. One study [10] compared the intervention with a 3 lux incandescent light and the other two studies [39,40] compared their intervention with a 200 lux fluorescent light of the identical colour temperature to their intervention light. Two studies delivered intervention light in an intermittent pattern [39,40], and one study administered the intervention light in a continuous manner [10], with a total duration of light exposure ranging from 4 to 6 h. A sleep restriction protocol was implemented in the study by Phipps-Nelson et al. [10], but not in the other two studies [39,40]. In the study by Phipps-Nelson et al., participants were allowed to sleep 5 h per night for the 2 nights prior. In terms of the prior light exposure, Smolders et al. [40] had participants undergo a 30-min adaption session under 200 lux light (same as their control light condition), Phipps-Nelson et al. [10] had their participants exposed to dim light (<5 lux) for about 6 h, and Huiberts et al. [39] implemented a 25 min adaption period using 100 lux light. Smolders et al. [40] and Huiberts et al. [39] measured subjective sleepiness by KSS (average score), and Phipps-Nelson et al. [10] measured subjective sleepiness by KSS (average score) and objective sleepiness using SEMs.

# Studies with non-significant alerting effect (N = 6)

The six studies that found non-significant results can be grouped according to the type of intervention light used. Two studies – one conducted by Munch et al. [41] and the other by Weisgerber et al. [42] – used broadband light of increased



Fig. 1. PRISMA flowchart for screening of literature.

illuminance as the intervention. Four studies, conducted by Sahin & Figueiro [43], Okamoto & Nakagawa [37], Segal et al. [35] and Alkozei et al. [33] respectively, used monochromatic blue light as the intervention. The characteristics of these studies are provided below with reference to the three studies that reported a significant alerting effect where applicable.

Munch et al. [41] study is comparable to the three studies that found a significant alerting effect regarding the timing of the light intervention and sleep history (see Table S1). Noticeable differences

between Munch et al. study and the three studies with a significant finding include the absence of a controlled adaption period before the light intervention, and that participants in this study were allowed to talk, read, write and listen to music during the intervention (Table S1). The intervention light used by Weisgerber et al. [42] had a much higher illuminance than that used in the three studies with significant results (5600 lux vs. 1000 lux). However, participants also had longer wakefulness (22 h vs. 4–5 h) before being exposed to the intervention light resulting in higher sleep

pressure, and were exposed to a shorter intervention light session (48 min vs. 5-6 h) compared to the three studies reporting a significant alerting effect. Furthermore, during light exposure, participants in Weisgerber et al.'s study were allowed to read and talk to the research assistant. Both of the studies measured subjective sleepiness only, using the KSS.

The irradiance/illuminance level of monochromatic blue light used was 40 lux in Sahin & Figueiro's study [43], 10 lux in Okamoto & Nakagawa' study [37],  $2.8-8.4 \times 10^{13}$  photons/cm<sup>2</sup>/s in Segal et al.'s study [35], and 214 lux in Alkozei et al.'s study [33]. The comparison light in these studies was 40 lux red light [43], 10 lux green and red light [37], 2.8–8.4  $\times$  10<sup>13</sup> photons/cm<sup>2</sup>/s green light [35], and 188 lux amber light [33], respectively. All four studies administered the light intervention over a single session, with the duration of the session ranging from 28 min [37] to 3 h [35]. A sleep restriction protocol was implemented in the study by Segal et al. [35], where participants were allowed 8 h sleep within the 48-h period prior to the intervention. Participants' regular sleep and wake schedule was used in the other three studies [33,37,43]. The duration of the dark/dim light adaption period varied among these studies, which were 10 min [37], 30 min [33], 42 min [43], and 3 h [35], respectively. Sahin & Figueiro [43] and Segal et al. [35] measured both subjective sleepiness using the KSS and objective sleepiness using EEG correlates. Okamoto & Nakagawa [37] and Alkozei et al. [33] measured subjective sleepiness using the KSS and SSS.

#### Studies with mixed results for alerting effect (N = 2)

Rahman et al. [34] and Sahin et al. [44] found a significant alerting effect of light for objective sleepiness measured by EEG correlates, but no difference for subjective alertness. Rahman et al. [34] compared a 6.5 h blue monochromatic light of 2.8  $\times$   $10^{13}$ photons/cm<sup>2</sup>/s with green monochromatic light of the same photon density from 4.75 h after participants' individual wake times. Participants restricted their total sleep time to 8 h over the 2 nights before light intervention. Also, a 4.75 h dim light (<3 lux) adaption was implemented. Results of this study indicated no difference in the KSS, but a significant reduction of theta-alpha power density (less sleepiness) in the blue light group. The study by Sahin et al. [44] included two experiments. One compared white light of 361 lux and 2568 K with ambient white light of <5 lux and 3500 K, and the other compared red light of 213 lux with ambient white light of <5 lux and 3500 K. Both of the experiments followed same protocol in that the participants maintained their regular sleep and wake schedule and underwent a dim light adaption period before the light intervention. Participants were exposed to a single 2 h light exposure session at one of three times (07:00-09:00 h; 11:00-13:00 h; 15:00-17:00 h). Neither intervention light influenced subjective alertness, but a reduction in alpha and theta--alpha power waves in the afternoon sessions, indicating an increased level of alertness, was found.

To summarise, it seems that fluorescent light of an illuminance of 1000 lux of more than 2 h duration is effective in promoting alertness levels during the daytime. In contrast, monochromatic blue light of low irradiance does not appear to be as effective in increasing alertness level during the daytime.

# Night time studies (N = 13)

Out of the 13 night time studies, five found a significant alerting effect of the intervention light [5,6,9,45,46], four studies found no alerting effect of intervention light [36,47–49], and the remaining four studies reported mixed results on the alerting effect depending on the measurement of alertness [28,38,50,51].

# Studies with significant alerting effect (N = 5)

All five studies used blue light of low irradiance; two studies used the monochromatic form [9,45], and the other three studies used the broadband form (blue light enriched with white light) [5,6,46].

In the two studies that used blue monochromatic light as the intervention, green monochromatic light of the same photon density  $(2.8 \times 10^{13} \text{ photons/cm}^2/\text{s})$  was the control [9,45]. In the study led by Lockley et al. [9], the duration of light intervention was 6.5 h for 1 session and for 1 night, and in the study by Cajochen et al. [45], the light duration was 2 h for 1 session and for 1 night. Dim light adaption was about 5 h in both studies. A notable difference is that Lockley et al. restricted participants' sleep time to 8 h over the 2 nights before the intervention [9], whereas Cajochen et al. asked their participants to follow their usual sleep and wake schedule [45]. Lockley et al. found a reduction in KSS scores, a decrease in delta—theta power densities, and an increase in the high range alpha waves. Cajochen et al. measured subjective sleepiness only, using the KSS; lower sleepiness was reported by the intervention group.

Of the three studies that used broadband blue light, the irradiance of the intervention light was about 40 lux [5,6,46], and that of control light varied from 1 lux [46] to 40 lux [5]. The duration of light intervention was 2 h for 1 night in Chellappa et al.'s study [5], 5 h for 1 night in Cajochen et al.'s study [6], and 4 h/night for 5 nights in Chang et al.'s study [46]. Participants in all three studies followed their usual sleep and wake cycle prior to the intervention light, and those in Chellappa et al. [5] and Cajochen et al.'s [6] studies went through a dim light adaption period. In all of the studies, the KSS was used to measure level of sleepiness, and a reduction in KSS score was found. In the study by Cajochen et al. [6], objective sleepiness was further measured by SEMs, and a reduced incidences of SEMs were also confirmed.

### Studies with non-significant alerting effect (N = 4)

Four night time studies [36,47–49] failed to observe a significant alerting effect of the intervention light. Rangtell et al. [47] compared reading on an electronic device (102 lux, 7718 K) with reading a physical book under ambient room light (67.3 lux, 2674 K). The light exposure session was 2 h for 1 night. This study was comparable to the three night time studies [5,6,46] that found a significant result regarding alerting effect of light, except for the adaption period. The light condition for their adaption period was 500 lux and of 6.5 h duration [47], instead of dim or dark adaption reported in the three significant studies [5,6,46].

In the other three studies with non-significant results, short to medium wavelength filtered white light was compared with full spectrum white light of different illuminance levels [36,48,49]. Van der Werken et al. [48] compared <530 nm filtered white light (193 lux) with full spectrum white light (256 lux); Rahman et al. [49] compared <480 nm filtered (439 lux) and <460 nm filtered white light (459 lux) with full spectrum white light (513 lux), and Sasseville at al. [36] compared <530 nm filtered white light with full spectrum white light (approx. 1200 lux). In these studies, the intervention light contained less short wavelength (e.g., blue) light as well as having a lower illuminance level compared to their respective control light conditions. The duration of the light exposure was 8 h for 2 nights in the study by van der Werken et al. [48], 12 h for 1 night in the study by Rahman et al. [49], and 30 min for 1 night in the study by Sasseville at al. [36]. Using subjective sleepiness as the outcome measure, none of these studies found a significant difference across conditions.

Studies with mixed results for alerting effects (N = 4)

The four studies with mixed results for the alerting effect of light varied in terms of the physical properties of the intervention light.

Van der Lely et al. [51] used a similar approach to the two studies discussed earlier [48,49], in that the authors compared filtered white light exposure to full spectrum white light. In this study [51], the light intervention was achieved by asking participants to wear blue blocker glasses from 18:00 h until bed time for 1 wk at home, then 1 night in the laboratory. Those in the control group were exposed to the full spectrum of white light by wearing normal glasses. The illuminance level was 106 lux for the intervention, and 103 lux for the control condition. Measurements of both subjective and objective sleepiness were only assessed on the laboratory night, thus the results might reflect an accumulative alerting effect. The authors found a higher level of subjective sleepiness (KSS) in the intervention group, but no difference for any EEG correlates.

In the study by Phipps-Nelson et al. [38], low irradiance monochromatic light (1.12–1.15 lux) for 6 h for 1 night was compared with low irradiance white light (0.02–0.2 lux). Participants underwent an 8 h dim light adaption, and followed their usual sleep and wake schedule the night before the intervention. Using this protocol, the authors found no difference in subjective sleepiness as measured by KSS, but a significant reduction in theta and delta wave activities as well as SEMs incidences, suggesting a reduced level of sleepiness.

Lastly, two studies compared white light of moderate illuminance (2500–3000 lux) with red light of low illuminance (4–24 lux) [21] and white light (120 lux) [31], respectively. In the study by Yokoi et al. [28], the duration of the light intervention was 7.5 h for 1 night. In the study by Lavoie et al. [50], the duration of the light intervention was 4 h for 1 night. Participants in both of the studies went through several hours of dim light adaption and followed their regular sleep and wake schedule before their light intervention. Yokoi et al. [28] reported no difference in the mean subjective sleepiness measured by KGS, but an increase in alpha wave activity at rest, which is an indicator of reduced sleepiness. Lavoie et al. [50] also failed to find a difference in subjective sleepiness using a VAS, but they reported a reduction in beta wave activity.

Taken together, blue light of low irradiance appears to be an effective measure in promoting alertness levels at night time in both monochromatic and broadband form. In contrast, white light of moderate illuminance was only effective in modulating objectively measured alertness levels. It appears that effective light treatment profiles differ diurnally. More importantly, subjective sleepiness measure seems to be less sensitive than objective sleepiness.

# Alerting effect of light **post** illuminance: day & night time studies (N = 14)

Among the 14 studies that examined the post-illuminance alerting effect of light, five studies were RCTs [10,33,35,52,53], and the other nine studies used a crossover design. Participants were mostly young and healthy adults, aged between 20 and 30 y, except in one study, where some participants were aged in their 40 s [38]. Sample size varied between 8 [38] and 90 [54], with many samples comprising 10 to 20 participants.

Studies investigating the alerting effect of light post-illuminance can generally be classified into three groups based on the time point when measurement of alertness occurs. The first group measured post-illuminance alertness within 24 h after the light intervention before a sleep episode; the second group measured alertness within 24 h after experimental light exposure, but after a sleep episode; and the third group measured alertness beyond 24 h post-light intervention.

# Post-illuminance alertness within 24 h before a sleep episode (N = 10)

Of the 10 studies in this group, six were undertaken during the daytime [10,33,35,41,42,55], and four were carried out at night [38,45,50,54]. The six daytime studies are detailed first, followed by the four night time studies.

# Daytime studies (N = 6)

Of the six daytime studies, post-illuminance alertness was measured 2 min [55], 44 min [42], 2 h [33,41], 3 h [35] and 4 h [10] after the completion of the light intervention. The three studies that measured alertness at 2–3 h post-illuminance observed no alerting effect of light [33,35,41], yet it should be noted that these studies observed no *during illuminance* alerting effect in the first instance. In the study by Phipps-Nelson et al. [10], the significant *during illuminance* alerting effect disappeared at the 4-h post-intervention timepoint. In the study by Weisgerber et al. [42], no *during illuminance* alerting effect was recorded at 44 min after the completion of light intervention. Finally, a significant reduction of sleepiness was demonstrated 2 min after the light exposure by Leichtfried et al. [55].

The two studies reporting a significant post-illuminance alerting effect used moderate to high illuminance (1000 lux and 5000 lux) polychromatic light as the intervention [42,55], and low illuminance white light as the comparison (400 lux and <50 lux). Leichtfried et al. [55] exposed participants to 5000 lux fluorescent light from 07:40 to 08:10 h for 1 d, and Weisgerber et al. [42] exposed participants to 48 min of 5600 lux for 1 d after 22 h of wakefulness. Participants in Weisgerber et al.'s study were allowed to talk and watch a movie during the light intervention, but then these activities were discouraged during the 44 min driving test immediately following the light intervention [42].

The characteristics of the four studies with a non-significant post-illuminance alerting effect of light have been discussed earlier. To reiterate briefly, two studies used monochromatic blue light as the intervention [33,35], one study used daylight as the intervention [41], and the other study used high illuminance white light as the intervention [10]. The light exposure duration was 30 min for 1 d in the study by Alkozei et al. [33], 3 h for 1 d in the study by Segal et al. [35], 6 h for 1 d in the study by Munch et al. [41], and 5 h for 1 d in the study by Phipps-Nelson et al. [10]. The post-illuminance alerting effect was measured under <2 lux light in Segal et al.'s study [35], <6 lux light in Munch et al. study [41], <5 lux light in Phipps-Nelson et al.'s study [10] and not reported by Alkozei et al. [33].

Night time studies (N = 4)

Of the four night time studies, the post-illuminance alertness level was measured at 45 min [54], 90 min [45], 1 h [50] and 2.5 h [38] after the completion of light exposure. A significant post-illuminance alerting effect was reported by Karchani et al. [54] and Phipps-Nelson et al. [38]. The remaining two studies reported no post-illuminance alerting effect.

In the study by Karchani et al. [54], participants were exposed to 2500–3000 lux fluorescent light during 15 min work breaks with 4 breaks per night over 2 night shifts. The post-illuminance alerting effect was measured by the KSS 45 min after the light intervention under normal room light. No alerting effect during illuminance was obtained. Phipps-Nelson et al. [38] measured the *during illuminance* alerting effect of light both subjectively and objectively. They used

blue light of a very low irradiance level as the intervention. Compared with white light of lower irradiance, a reduction in SEM incidences and theta waves was recorded during illuminance, and sustained over the 2.5 h post-illuminance in a similar light condition to their control.

Unlike the study by Phipps-Nelson et al. [38], the positive alerting effect found during illuminance in the studies by Cajochen et al. [45] and Lavoie et al. [50] both disappeared after the completion of light exposure. Cajochen et al. compared mono-chromatic blue light with green light ( $2.8 \times 10^{13}$  photons/cm<sup>2</sup>/s), and Lavoie et al. compared white light of increased illuminance (2300–4700 lux) with red light of low illuminance (4–24 lux).

# Post-illuminance alertness within 24 h, but after a sleep episode (N = 2)

Two studies investigated the alerting effect of light after one night's sleep. Both studies compared reading from an electronic device with reading a physical book [46,47]. Results are mixed in terms of the alerting effect post-illuminance. In the study by Chang et al. [46], participants who read using an electronic device had less polysomnography (PSG) measured SEMs, prolonged sleep latency and reduced theta/alpha waves before sleep onset, and a higher level of sleepiness upon wakening.

Likewise, Rangtell et al. [47] assessed PSG measured sleep latency and EEG correlates after sleep onset, and subjective sleepiness via the KSS upon wakening, but the authors did not find a statistically significant difference in any of these aspects. Rangtell et al.'s [47] study differed from Chang et al.'s study in several ways; using a shorter duration of light exposure (2 h vs 4 h), less nights of light exposure (1 night vs. 4 nights), and a higher illuminance light condition for the adaption period (500 lux vs. ~90 lux).

### Post-illuminance alertness beyond 24 h (N = 2)

Mixed results were found regarding the alerting effect of light beyond 24 h. In the study by Horowitz et al. [53], participants were exposed to 2500 lux fluorescent light for 6 h over 3 nights, and a significant reduction in subjective sleepiness measured by a VAS on day 1 and day 2 after illuminance was revealed. Thessing et al. [52] reported two experiments with an identical protocol except for the duration of the light exposure. Participants in one experiment were exposed to a very high illuminance light (8000–9000 lux) for 2 h for 1 night, and those in the other experiment were exposed to the same light intervention for 4 h for 1 night. Post-illuminance alertness were measured by VAS and MSLT on the following night. The 2 h light exposure did not affect subjective or objective sleepiness. The 4 h light exposure shortened the sleep latency at one time point, but was not effective in reducing mean subjective sleepiness.

To summarise, the acute alerting effect of light does not seem to sustain after the light intervention, but it is possible to alter one's alertness level by phase shifting their circadian rhythm.

## Discussion

The current systematic review identified a diurnal pattern in what constitutes an effective light intervention for reducing sleepiness. Blue light of low irradiance is clearly effective in reducing sleepiness during biological night, but its influence on alertness during the day is much less evident. In contrast, white light of moderate illuminance intensity is effective in reducing subjective sleepiness during the day. However, it is not effective in reducing subjective sleepiness at night, although an alerting effect was observed when an objective measure of alertness, such as EEG, was used. Most studies included in this review were conducted under controlled laboratory conditions, where environmental stimuli are minimised; thus limiting the generalisability of the findings to industry settings.

# Modulation of circadian rhythm, sleep homeostatic pressure and light intensity

Among healthy, rested and room light adapted volunteers, a 1000 lux white light was shown to be more effective in reducing subjective sleepiness than 150-200 lux white light during the daytime [39,40], except for the study by Munch et al. [41]. The two studies that reported a superior alerting effect had either the same correlated colour temperature between intervention and control groups (4000 K) [39], or lower colour temperature in the intervention (4000 K) than the control (6500 K) [40]. In the study by Munch et al. [41], the intervention light source used was daylight and/or fluorescent light to generate an intensity of 1000 lux depending on the time of the day. Therefore, it is reasonable to assume that the colour temperature of the intervention light would be cooler than that of the control light source (3700 K). Had participants not been exposed to daylight on the commute to the laboratory, an alerting effect might have been observed in the intervention group. In contrast to daytime studies, a 2800 lux white light made no difference to subjective sleepiness compared to a 120 lux white light during biological night among similar participants [28]. In this study, although both control and intervention lights were generated by fluorescent light tubes, it was not stated whether the same type of fluorescent tube was used for both conditions. Regardless, the available evidence seems to suggest that the minimum light intensity required to stimulate a subjective feeling of alertness is much higher during the day due to low sleep pressure and a rising circadian drive. At night, sleep pressure has accumulated, which in combination with a decreasing circadian drive results in a lower alertness level, which means people may be more sensitive to light intervention. The differing threshold in light intensity seems to fit well with the two-process sleep model [56]. As indicated by the results of an earlier study on the dose-response relationship of white light on alertness at biological night, although a 230 lux white light was superior to 23 lux white light, a further increase to 3190 lux did not result in a further reduction in either subjective or objective sleepiness [17]. In contrast to our results, Ruger et al. found that a 5000 lux white light was effective in reducing subjective sleepiness both during the day and at night compared to a <10 lux white light [57]. Yet, it should be noted that participants in their study went through a dim light adaption, and more importantly, a much lower intensity control light condition. Prior light exposure or darkness exposure, as discussed later in detail, does impact the effectiveness of light intervention on alertness. Although a dose-response relationship has been demonstrated during biological night, this relationship has not been examined during the daytime. Further, how this dose-response relationship varies according to wavelength is unknown.

# Modulation of circadian rhythm, sleep homeostatic pressure and light wavelength

The present review clearly shows that low irradiance blue light was more powerful in reducing subjective sleepiness than monochromatic green light of the same photon density during biological night in both rested [45] and sleep deprived participants [9]. This observation is consistent with the findings of a rodent study carried out by Pilorz et al. [58], where high intensity blue light produced a greater arousing effect in mice as manifested by delayed sleep onset, behavioural aversion and high corticosterone levels in nocturnal mice compared to green light of the same photon density during night time. Different to the night time studies presented in this review, low irradiance blue light was not more alerting than green light of the same photon density when applied during the daytime [35,37]. This diurnal difference in relation to the alerting effect of different spectrums can be explained by the three-process model of sleep regulation developed by Hubbard and colleagues [11,59]. Light is alerting in humans, and according to this model, at night, blue light stimulates the melanopsin receptor that plays a dominant or sole role in activating the circadian rhythm, sleep pressure and direct effect processes, whereas green light only makes a small contribution to the alerting effect of light via the direct effect process and circadian rhythm mediated by rods and cones. During the daytime, green light takes a major role in increasing alertness level via rods and cones via the direct effect pathway. The alerting effect produced by green light may be equivalent to the alerting effect produced by blue light through melanopsin via the circadian rhythm. This might explain the non-significant differences seen between blue and green light during the day.

#### Other influencing factors for alertness

Most of the included studies examined healthy participants with non-extreme chronotypes, except for the study by van der Lely [51], where participants were adolescents with moderate to extreme evening chronotypes. Chronotype has been identified as a personal trait that modulates the alerting effect of light. As summarised by Gaggioni et al. [60] in relation to cognitive function, during biological night, blue light is less beneficial for participants with an evening chronotype than for participants with a morning chronotype, because participants with evening types have a stronger compensation mechanism to oppose the adverse effect of a combination of a low circadian drive and high sleep pressure than participants with morning types. The inclusion of participants with a moderate to extreme evening chronotype in van der Ley's [51] study might explain why no differences in EEG data were observed between the filtered blue light and full spectrum white light conditions. However, it is hard to explain why a significant reduction in subjective sleepiness was observed in the filtered blue light condition.

During the assessment of sleepiness, most of the included studies required that participants simultaneously completed monotonous activities. For three studies [28,41,42], participants were allowed to speak with each other or a research assistant. Talking to other people is known to promote greater alertness compared to sitting alone [61], because during an executive task, thalamus, a key brain structure linking alertness and cognition [8] is consistently recruited. This might explain the findings of Weisgerber et al. where no difference in alertness was found during the light intervention when participants were allowed talk; and yet a significant alerting effect was seen 45 min after the light exposure [42].

#### Waking EEG correlates in relation to process C and process S

Among studies where EEG correlates were used as an objective measurement for sleepiness, alpha, theta and delta bands were measured. In the studies included in this review, the definitions used for these wave bands were very similar to those proposed by Cajochen and colleagues [29], with alpha defined as 8–12 Hz, theta as 4–8 Hz, and delta as 1–4 Hz. Some combined wave bands of alpha and theta were also used [34,43,44,50], and in two studies, specific wave activity was not differentiated due to an overall non-significant finding [35,51]. Both subjective and objective measures of sleepiness (e.g., EEG correlates) measure a state of drowsiness [20]. These measures demonstrate high agreement. When the presence of an alerting effect of light differs according to the measurement type, it is usually the case that the objective measurement, but not subjective measures, demonstrates an alerting

effect [34,38,44]. This pattern seems to indicate that subjective measures are less sensitive to changes in alertness compared to objective measures. In the current review, the only exception to this pattern is van der Ley's [51] study where a difference in subjective alertness was observed when no effect on EEG was found.

#### Prior light exposure/sustained alerting effect of light

Some preliminary conclusions about the post-illuminance alerting effect of light can be drawn from this review. First, prior light exposure does seem to attenuate the alerting effect of the light intervention. For example, in the study by Rangtell et al. [47], 102 lux light of a colour temperature of 7718 K failed to elicit an alerting effect compared to a 67.3 lux light of 2674 K, whereas other similar studies [6,46] observed a significant alerting effect. This is likely to be associated with the 6.5 h of 500 lux prior light exposure. Prior daylight exposure is also likely to be explanation for the non-significant alerting effect of the intervention light observed in Munch et al. study [41]. A similar effect has also been demonstrated in rodent models, where the effect of the light/dark cycle extends for several hours [62]. Second, the time of day that the alerting effect was measured is likely to have moderated the post-illuminance alerting effect of light. In the daytime study by Phipps-Nelson et al. [10], the non-significant post-illuminance alerting effect was measured at 21:00 h when the circadian drive for alertness was at its highest (for participants without extreme chronotypes [56]), which might have masked the post-illuminance effect. In their night time study [38], the post-illuminance alerting effect was measured at 09:30 h in almost complete darkness, and the reduction of delta, theta waves and SEMs observed during blue light condition persisted. Together, these results lend support to the notion that an alerting effect of light can be sustained beyond the immediate light exposure (see also Hubbard et al. [11]). To date, many of the studies that examined the post-illuminance alerting effect of light have measured this effect under a dim light condition, where the alerting effect of light dissipates quickly. However, these conditions do not mimic those of industry and such dim lighting are rarely seen in some workplaces such as hospitals. Therefore, future research should also investigate the optimal light intervention for the purpose of producing an adequate post-illuminance alerting effect of light under room light conditions. This question is meaningful for the health industry in particular, where staff and patients require different light/darkness exposure, especially at night. Tanaka et al. [63] reported that a 10 min bright white light exposure was effective in reducing subjective sleepiness at 3 h post-illuminance under room light conditions when completing normal work activities, but this study was not included in this review because the light properties of the intervention were not reported.

#### Risk of bias assessment results

Overall, the studies included in this review demonstrated high internal validity. As indicated in Figs. 2 and 3, it is common for studies to not report information that allows for the assessment of the risk of bias associated with random sequence generation, allocation concealment and outcome assessment. However, we stress the difference between reporting and executing, and therefore, our assessment of bias may overestimate the risk of bias. With regard to the crossover trials, the proportion of studies reporting the results of an assessment of possible carryover effects was low. Furthermore, paired analysis was used in all but two studies [49,55]. Yet, the use of unpaired analysis is likely to result in an underestimation of the true effect size. Therefore, it may be that light intervention is more effective than indicated here.



Fig. 2. Assessment of risk of bias for randomised controlled trials (N = 8).



Fig. 3. Assessment of risk of bias for crossover studies (N = 20).

## Conclusion

Blue light of low irradiance is probably an effective light intervention for increasing alertness levels at night, but is less effective during the daytime. Moderate bright white light is likely to be effective in reducing sleepiness during the daytime, but might be less effective at night. Environmental factors (including prior light exposure) and individual factors (including chronotype and the activities undertaken during the measurement of sleepiness) influence the alerting effect of a light intervention. The development of light therapy as a sleepiness prevention strategy requires researchers not only to report the most complete form of the light's physical properties [13], but also to report other detailed information in relation to the third process that may contribute to sleep regulation in addition to process C and process S. Investigation of the dose—response relationship between specific light interventions and the alerting effect during the daytime and how this is influenced by spectral wavelength is also recommended. Knowledge gained from such research will eventually assist in the development and use of suitable light infrastructure and light interventions for various workplaces.

## **Practice points**

- The minimum light intensity required to induce an alerting effect is higher during the day than at night, and this minimum light intensity is likely to vary with the spectral distribution of light.
- Light's alerting effect is not only modulated by process C and process S, but also by the third process, which has been referred to as process A, or the direct effect of light.
- 3. The alerting effect of light is likely to be sustained beyond the light intervention, but its impact will be highly dependent on other factors.

#### **Research agenda**

- Investigate the dose-response relationship between various light properties and its alerting effect during the day to determine the minimum intensity required in relation to spectral wavelength distribution.
- Investigate the post-illuminance alerting effect of light, considering the circadian rhythm (process C), sleep homeostasis (process S) and other environmental stimuli and personal traits (the third process).
- 3. Explore the use of brief light interventions at the beginning of a work shift as a method to increase alertness during the work period.

## **Conflicts of interest**

The authors declare no conflicts of interests.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.smrv.2017.12.001.

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