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Individually tailored light intervention through closed eyelids to promote circadian alignment and sleep health

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ABSTRACT

Background: Light is most effective at changing the timing of the circadian clock when applied close to the core body temperature minimum. The present study investigated, in a home setting, if individually tailored light treatment using flashing blue light delivered through closed eyelids during the early part of the sleep period delayed circadian phase and sleep in a population of healthy older adults and in those suffering from early awakening insomnia.

Methods: Twenty-eight participants (9 early awakening insomniacs) completed an 8-week, within-subjects study. Twice, participants collected data during 2 baseline weeks and 1 intervention week. During the intervention week, participants wore a flashing blue (active) or a flashing red (control) light mask during sleep. Light was expected to delay circadian phase. Saliva samples for dim light melatonin onset were collected at the end of each baseline and intervention week. Wrist actigraphy and Daysimeter, a calibrated light and activity meter, data were collected during the entire study.

Results: Compared to baseline, flashing blue light, but not flashing red light, significantly ($P < .05$) delayed dim light melatonin onset. The mean ± standard deviation phase shift (minutes) was 0:06 ± 0:30 for the flashing red light and 0:34 ± 0:30 for the flashing blue light. Compared to day 1, sleep start times were significantly delayed (by approximately 46 minutes) at day 7 after the flashing blue light. The light intervention did not affect sleep efficiency.

Conclusions: The present study demonstrated the feasibility of using light through closed eyelids during sleep for promoting circadian alignment and sleep health.

Background

Humans are under the influence of two mechanisms: the homeostatic (sleep drive) and the circadian (alerting force) systems.[1,2] The sleep drive and the alerting force are distinct mechanisms, independent from each other, although they normally work together to ensure that we are asleep at night and awake during the day. Sleep drive is low when we wake up and increases steadily throughout the day, and then diminishes rapidly within the first hours of sleep. The alerting force is regulated by the biological clock and follows a daily, circadian rhythm. The biological clock sends the body an alerting signal during the daytime and a sleeping signal at night. The interaction between the sleep drive and the alerting force determines when we fall asleep and how well we sleep at night. Misalignment between these two systems will lead to disturbed sleep or to sleep times that are not optimum with societal norms, such as what may be experienced by those suffering from early sleep onset or from delayed sleep phase disorder.

The retinal light/dark exposure pattern is the main synchronizer of the circadian system to the local position on earth.[3] When this pattern is disrupted or misaligned with social requirements, a tailored light intervention can be used to promote sleep consolidation and efficiency by aligning the signals from the biological clock with the sleep drive mechanism, thus controlling the timing of the sleep/wake cycle.[4] The relationship between the timing of a light intervention and the changes (magnitude and direction) in circadian time is described by a phase response curve (PRC).[5] The point on the PRC where the application of a light stimulus changes circadian phase from maximum delay to maximum advance is known as the *crossover point*. In humans, this occurs near the time of the core body temperature minimum (CBT_{min}), which typically occurs during the latter portion of the sleep period and corresponds to when people are most sleepy. In an individual normally entrained to the local 24-hour light/dark cycle, evening light exposure (ie, prior to CBT_{min}) delays circadian phase, and morning light exposure (ie, after CBT_{min}) advances circadian phase.[5]

Because CBT_{min} occurs during sleep, the first challenge for applying light when it has the most impact on circadian phase is to determine eyelid transmittance. Robinson et al[6] were among the first to measure light transmission through human closed eyelids. Their results suggested that the eyelids function as a red-pass filter, with transmission of 14.5% of 700-nanometer (nm) light, but only 3% or less transmission of light at 580 nm and below. Similarly, Ando and

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Kripke[7] showed that red light (615-635 nm) was attenuated to 5%, whereas blue (400-510 nm) and green (540-565 nm) lights were attenuated to less than 1%.

Recently, Bierman et al[8] modeled the spectral transmittance of the human eyelid. Using predictions from their spectral transmittance model, Figueiro and Rea[9] used 527-nm (green) light-emitting diodes (LEDs) to deliver 60 minutes of continuous light to the eyelids of sleeping participants. Depending on the spectral transmittance of each participant's eyelids, it was determined that between 17 000 and 50 000 lux at the eyelid from the green LEDs was needed to reliably stimulate the circadian system as measured in terms of nocturnal melatonin suppression and of delaying circadian phase, as measured by dim light melatonin onset (DLMO).[9] Although effective, the heat generated by the continuously operated LEDs was very high and constituted a significant barrier to the development of a practical device that could be used at home to correct circadian misalignment.

Although the underlying retinal mechanisms responsible for photic stimulation of the circadian system are still under investigation, Rea et al[10,11] proposed a model of human circadian phototransduction. The intrinsically photosensitive retinal ganglion cell[12] is the central element in the phototransduction model, but it also receives input from classical photoreceptors.[13] Their proposed model was shown to be able to quantitatively predict light-induced nocturnal melatonin suppression from both narrow-band and polychromatic light sources.[9,14,15] Based on the phototransduction model, Figueiro et al[16] hypothesized that a train of brief flashes of short-wavelength (blue) light could provide photic information to the biological clock and phase shift DLMO. The advantage of delivering a train of brief flashes is the lack of heat buildup from the light source, which makes it possible to use this light mask at home. Figueiro et al[16] demonstrated, in a laboratory study, that 2-second pulses of a 480-nm light acutely suppressed melatonin and phase shifted DLMO. More recently, Figueiro et al[17] demonstrated, in a pilot study using 10 subjects, that 1-hour exposure to 2-second pulses of flashing blue light delivered every 30 seconds for 7 consecutive days phase delayed DLMO by about 24 minutes in those living at home. The present study extends those by Figueiro et al[16,17] by investigating if a flashing 480-nm (blue) light delivered through closed eyelids during the early part of the sleep period delayed circadian phase and sleep start times in a population of healthy older adults and in those suffering from early awakening insomnia.

Unlike the previous published studies,[16,17] the present study used a flashing 640-nm (red) light mask as the control condition. Another novelty of the present study was that data from a calibrated light measuring device worn by subjects were used in combination with an algorithm to make daily adjustments to the timing and duration of light exposures to more effectively achieve a target circadian phase delay. In addition, this is the first field study that tested the effectiveness and feasibility of delivering a light treatment through closed eyelids during sleep in a group of early awakening insomniacs. It was hypothesized that circadian phase, as measured by DLMO, and sleep start and end times, as measured by actigraphy, would be significantly delayed after the flashing blue light but not after the flashing red light. The use of flashing light rather than continuous light exposures is practical because its brief duration reduces the blue light hazard risk[18] and reduces heat generation, which is one of the major barriers for the development of a commercial light mask product.

Methods

Participant selection

Twenty-nine participants over the age of 65 years were recruited through email and posted notices. Nineteen participants (mean age ± standard deviation [SD] = 69 ± 5 years; 9 men) were healthy older adults who did not report having early awakening insomnia, and 10 participants (mean age ± SD = 70 ± 4.5 years; 2 men) reported a history of early awakening insomnia. No *a priori* power calculations were performed. One early awakening participant withdrew, and his data are not reported here. Participants were not included in the study if they had sleep apnea, restless legs syndrome (RLS), or cognitive impairment or if they reported using β-blockers. Sleep apnea was screened for using the Sleep Apnea Scale of the Sleep Disorders Questionnaire, a 12-item scale, yielding scores between 0 and 60. A score of 29 was used as a cutoff for men (sensitivity 75%, specificity 65%), and a cutoff of 26 was used for women (sensitivity 80%, specificity 67%).[19] RLS was screened for using the RLS Rating Scale, a 10-item scale that yields scores between 0 and 40. A cutoff of ≥11 (indicating the presence of symptoms that are at least moderate) was used as a positive screen for RLS.[20] The cognitive status exclusion criterion consisted of a score of 24 or less on the Mini-Mental State Examination.[21]

Normal sleepers were healthy older adults who reported going to bed after 21:00 and waking up after 05:30. Early awakening insomnia was characterized using self-reports. Potential participants who complained that they could not stay awake past 19:00 (even though their actual bedtimes during the study weeks may have been later) and could not stay asleep past 04:00 (even though their wakeup times during the study weeks may have been later) were accepted into the study. All of the early awakening insomniacs had Pittsburgh Sleep Quality Index (PSQI) scores greater than 6. Five normal sleepers had PSQI scores between 6 and 9. All other normal sleepers had PSQI scores less than 6. The mean ± SD PSQI[22] scores were 4.6 ± 2.8 for the normal sleepers and 10.5 ± 3.2 for the early awakening insomniacs. The mean ± SD self-reported bedtimes and wakeup times (hours:minutes) from sleep logs kept during the weeks of the experiment for the normal sleepers were 22:18 ± 1:11 and 06:24 ± 1:01. The mean ± SD self-reported bedtimes and wakeup times for the early awakening insomniacs were 20:12 ± 0:56 and 04:22 ± 0:54. All participants provided written informed consent approved by Rensselaer Polytechnic Institute's Institutional Review Board and were paid for their participation. The study was conducted in accordance with the Declaration of Helsinki[23] and conformed to international ethical standards.

Light conditions

Active light was delivered to both retinae through closed eyelids using the flashing blue light mask previously described by Figueiro et al[16] and shown in Figure 1. In brief, the active light mask contained two blue LED arrays (wavelength of peak intensity [λ_{max}] = 480 nm, full-width-half-maximum [FWHM] = 24 nm), one for each eyelid. Using the elastic strap around the back of the head, the light mask held the LED arrays in front of the eyelids. A control light mask containing two red LED arrays (λ_{max} = 640 nm, FWHM = 25 nm) was used. The light-stimulus condition was a train of blue or red light pulses: 2-second duration light pulses spaced apart 30 seconds for no more than 3 hours. The light mask was programmed to be turned on no earlier than 1 hour after bedtimes and to be turned off no later than 1 hour prior to CBT_{min}, which was estimated to occur 7 hours after baseline DLMO. Therefore, the train of light pulses always occurred during the expected delay portion of the PRC. A target phase shift of 2 hours was established at the start of the study. Every evening, participants were asked to report their expected bedtimes and to download the light data from the Daysimeter to a laptop that was provided to each participant. Once the download was complete, a modified algorithm based on the model of human circadian entrainment by Kronauer et al[24] was used to program the most effective timing to apply circadian light, each night, using the active light