

Light and chronobiology: implications for health and disease

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Environmental light synchronizes the primary mammalian biological clock in the suprachiasmatic nuclei, as well as many peripheral clocks in tissues and cells, to the solar 24-hour day. Light is the strongest synchronizing agent (zeitgeber) for the circadian system, and therefore keeps most biological and psychological rhythms internally synchronized, which is important for optimum function. Circadian sleep-wake disruptions and chronic circadian misalignment, as often observed in psychiatric and neurodegenerative illness, can be treated with light therapy. The beneficial effect on circadian synchronization, sleep quality, mood, and cognitive performance depends on timing, intensity, and spectral composition of light exposure. Tailoring and optimizing indoor lighting conditions may be an approach to improve wellbeing, alertness, and cognitive performance and, in the long term, producing health benefits.

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Dialogues Clin Neurosci. 2012;14:448-453

Keywords: circadian rhythm; daylight; bright light; indoor lighting; zeitgeber; entrainment; intrinsically photosensitive retinal ganglion cell (ipRGC); light therapy; circadian rhythm sleep disorder; affective disorder

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Introduction

The solar 24-hour cycle has existed for more than 4 billion years, and it has led to the evolution of circadian rhythms in most organisms. In mammals, a circadian master clock in the brain has evolved in the suprachiasmatic nuclei (SCN) of the mammalian hypothalamus.¹ This master clock has a genetically determined endogenous period length which slightly differs from 24 hours² and has to be adjusted to the exact 24-hour rhythm day by day. Environmental light is the strongest synchronizer for the circadian system, and phase-resetting capacities to light mainly depend on time of day, light intensity, and spectral composition.³ *Table 1* illustrates illuminance ranges (lx) under different natural and electrical lighting conditions.

Under controlled laboratory conditions, the impact of timing light exposure has been shown to shift the human biological clock, as illustrated in the phase-response curve to light (*Figure 1*).⁴ The strongest circadian phase delays were induced when light exposure occurred in the evening or night hours before the core body temperature nadir (usually around 5 am). Maximum advances occurred in the early morning hours after the core body temperature minimum, whereas around noon, bright

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light exposure exerted only small effects. The impact of light intensity on circadian phase was studied using light pulses from 0.1 to 10 000 lx to describe and quantify dose-response curves.^{5,6} When different light intensities

Environmental lighting situation	Typical illuminance range [lx]
Daylight, clear sky	50 000-100 000
Daylight, overcast sky	10 000-20 000
Light therapy lamp	5000-10 000
Precise indoor workbench	1000-2000
Typical indoor office setting	300-500
Living room lighting	50-200
Street and walkway lighting	5-20
Full moonlight	< 1

Table 1. Approximate illuminance ranges of different lighting environments (measured on a horizontal plane). Illuminance indicates the flux density of a light source and is measured in lux (symbol: lx). Lux is defined as lumen per unit area (lumen per square meter: 1lx=lm/m²). Please note that in most cases, where the light source is located above a human observer, much less illuminance is measured on a vertical plane at the approximate eye level (viewing direction).

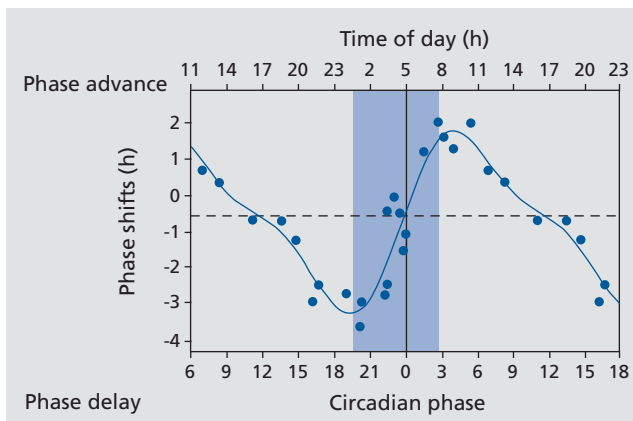


Figure 1. The human phase response curve, where phase advances are indicated with positive values, and delays with negative values. The data are plotted against the timing of the center of the light exposure, relative to the melatonin midpoint on the pre-stimulus circadian phase assessments (defined to be 22 h). Data points from circadian phases 6 to 18 are double plotted. The filled circles represent data from melatonin samples. The solid curve is a dual harmonic function fitted through all of the data points. The horizontal dashed line represents the anticipated 0.54-h average delay drift of the pacemaker between the pre- and post-stimulus phase assessments. The vertical line represents the core body temperature minimum (= circadian phase 0), and the grey bar. Adapted from ref 4: Khalsa SB, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. *J Physiol.* 2003;549(Pt 3):945-952. Copyright © Cambridge University Press 2003

and durations were combined, longer exposures with moderate light intensity resulted in larger phase shifts than shorter exposures to brighter light.⁷ Most recently, a duration-response curve to a single bright light pulse of 10 000 lx demonstrated a nonlinear relationship for circadian phase shifts in humans after different durations (0.2 h to 4 h).⁸ Shorter light exposures were more effective.

Light through the eyes is perceived by rods, cones, and also intrinsically photosensitive retinal ganglion cells (ipRGC)^{9,10} (Figure 2) containing the photopigment melanopsin. Only 1% to 2% of ipRGCs are directly light-sensitive, and to date five subtypes of ipRGCs (M1-M5) are anatomically and functionally distinguishable.¹¹ The ipRGCs integrate incoming light information in two different ways: directly by intrinsic photosensitivity and via afferent synaptic input from rods and cones. Melanopsin-dependent neuronal projections connect the retina with deeper brain areas such as the SCN, the pre-tectal olivary nucleus (pupillary light reflex), pineal gland, habenula, thalamus, and many more.^{12,13} The ipRGC's response is shifted towards the blue light spectra, showing a sensitivity peak around 480 nm, whereas the photopic sensitivity maximum of the three types of cones is in the green part of visible light (at 555 nm).¹⁴

Acute light effects

Light also exerts acute effects on subjective alertness and cognitive performance, and it inhibits the secretion of melatonin by the pineal gland.^{3,5,15,16} Salivary or plasma

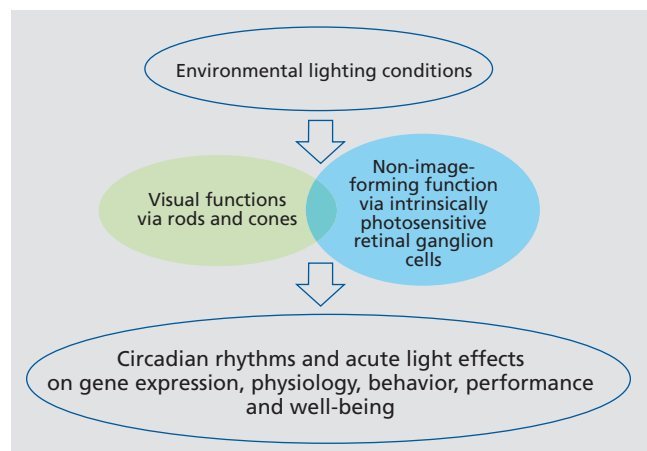


Figure 2. Schematic summary of the general impact of light on both visual and non-image-forming biological functions.

Brief report

melatonin concentrations are commonly used to assess circadian phase or to quantify the magnitude of light-induced melatonin suppression. Acute light effects are dependent on the photopigment melanopsin, and are stronger when light contains a greater proportion of blue light.^{3,17} For example, light exposure with monochromatic blue light had a greater alerting effect, increased heart rate, core body temperature, cognitive performance, pupil light reflex, and clock gene expression compared with green light (for reviews see refs 3,17). Several functional magnetic resonance imaging (fMRI) studies have revealed higher brain activity¹⁶ and stronger effects on mood-related brain areas to monochromatic blue than to green light.¹⁸ Even a low-lit computer screen, which contains more blue light, had stronger effects on subjective alertness and cognitive performance than a conventional screen.¹⁹ Most of these studies were performed during nighttime, with prior dim or dark adaptation. Some also showed acute light effects during daytime and evening with polychromatic white light²⁰⁻²² or blue-enriched light sources.^{23,24} Acute light effects are at least partly conveyed by the ascending reticular arousal system, projecting to higher cortical areas via the brain stem, hypothalamus, thalamic nuclei, and other brain regions,^{16,22} known to convey visual and nonvisual information (such as the lateral geniculate nuclei of the thalamus²⁵). There is growing evidence that genetic factors, for example the clock gene *PER3* polymorphism, play a role in responsiveness to acute light effects in humans.²⁶ Prior light history modulates subsequent light effects, as has been shown on circadian phase shifts, melatonin suppression, and cognitive performance.²⁷⁻²⁹ Light exposure during the day impacts on sleep during the night,³⁰ with different effects on sleep latency, non-rapid eye movement sleep, slow-wave activity, and wakefulness during scheduled sleep, as well as on rapid eye movement sleep latency. These changes depend on the light source, exposure duration, and timing.³⁰⁻³²

Light and age

There is conflicting information as to whether healthy older adults undergo a general attenuation in non-image-forming light perception. At the level of the eye, a substantial proportion of visible blue light is filtered out due to physiological yellowing of the aging lens and smaller baseline pupil size.³³ Some evidence for functionally intact (blue) light sensitivity with age comes

from a recent study, in which steady-state pupil constrictions to monochromatic blue light were similar in young and older subjects.³⁴ Another study showed that sustained pupil contraction to a bright blue light stimulus increased, and redilation to baseline took longer, in older than younger subjects.³⁵ This may indicate a compensatory response to the lower blue light transmission through the aging lens. The fact that older patients with cataracts exhibited faster reaction times under blue-enriched light after cataract surgery (with clear UV-only blocking intraocular lens replacement) when compared with presurgery performance³⁶ indicates that attenuation of blue light sensitivity might be an epiphenomenon caused by reduced light transmission of the lens, and not by a change in sensitivity of melanopsin-dependent function itself.

Likewise, older subjects suppressed melatonin less in response to monochromatic blue than green light^{37,38} and exhibited reduced responsiveness with respect to mood and alertness when compared with a young group.³⁷ Healthy older subjects showed a reduction in the phase-delaying response to moderate light³⁹ and, evening exposure of healthy elderly subjects to either polychromatic blue-enriched or polychromatic white light did not differ in its effects on phase delay, evening alertness, and sleep architecture.⁴⁰ One interpretation might be that non-image-forming light perception undergoes different age-related modifications of functionally separated ipRGC dependent pathways.

Light treatment of misaligned circadian rhythms

Scheduled bright light exposure is an effective countermeasure for sleepiness and fatigue, ie, in shift workers during night work and for re-entrainment after return to daytime shifts, or jet lag. Other circadian rhythm sleep disorders, such as delayed and advanced sleep phase syndrome, can be treated with light therapy as well (for reviews see refs 41,42). Light therapy is used alone or as adjuvant therapy in a growing number of psychiatric and neurodegenerative diseases, where alterations of sleep-wake cycles are often observed.⁴³⁻⁴⁵ Light has antidepressant properties and is the treatment of choice for seasonal affective disorder (SAD),⁴⁶ and is increasingly used in nonseasonal depression,⁴⁵⁻⁴⁷ particularly efficient when combined with serotonin reuptake inhibitors.⁴⁸⁻⁵⁰ Moreover, beneficial effects of light on mood, agitation,

sleep quality, and/or cognitive performance have been found in patients with ante-partum depression,⁵¹ borderline personality disorder,^{52,53} bulimia nervosa,⁵⁴ adult attention-deficit/hyperactivity disorder,⁵⁵ and Parkinson's disease⁵⁶ as well as Alzheimer's disease and other dementias,^{57,58} by applying open trial designs and double-blind protocols. The control condition in those studies was either no light treatment, or lower light intensities (ie, 70 lx,⁵¹ 500 lx red light⁵⁴), or lower lighting (± 300 lx) compared with whole-day bright lighting installations (± 1000 lx) in elderly care units.⁵⁸ Regular outdoor morning light exposure has led to similar antidepressant effects in SAD as with artificial light therapy.⁵⁹

Optimizing indoor lighting conditions

Despite the multitude of studies investigating light effects on humans, it is still unclear how much light is needed during daytime to stay fully entrained to the environmental light-dark cycle. This becomes an important topic in our round-the-clock society, since the time we spend outside during the day progressively decreases, whereas the time we spend with light-emitting devices during the night increases. Another factor is the substantial interindividual difference in light requirements by the circadian system to stay synchronized with the external 24-hour rhythm, for example between extreme morning or evening types ("larks" and "owls"). The def-

inition of extreme chronotypes is based on subjective preferences for very early (morning type) or very late (evening type) habitual sleep and wake (times), which usually differ by 2 to 4 hours.⁶⁰ Both chronotypes are usually obliged to follow similar scheduled work hours in spite of being at different endogenous circadian phases,⁶⁰ and thus, respond differently to the daytime light exposure, which has to be considered when designing indoor lighting conditions.

Conclusion

Chronobiological knowledge of how light affects human behaviour has begun to be implemented at work places,²⁴ in schools,⁶¹ and in clinical environments (such as residential care homes for the elderly, and intensive care and neonatal units^{24,51}). There is still much work to do: to test, predict and apply optimal lighting conditions for different populations and patients, in terms of spectral composition, light intensity, and dynamics. Also, geographical latitude, building exposure, and building properties play an important role. Only synergistic interdisciplinary work between (neuro-) scientists, physicians, architects, and engineers will allow us to better assess and optimize lighting conditions, and to foster the translation into practical applications. □

Acknowledgments: Dr M. Münch is supported by the Velux Foundation (Switzerland), and Dr V. Bromundt by the AXA Research Fund.

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Brief report

Luz y cronobiología: efectos en la salud y la enfermedad

La luz ambiental sincroniza el reloj biológico primario de los mamíferos en el núcleo supraquiasmático, así como muchos relojes periféricos en tejidos y células, para el día solar de 24 horas. La luz es el agente sincronizador más potente (zeitgeber=dador de tiempo) para el sistema circadiano, y por consiguiente mantiene la mayoría de los ritmos biológicos y psicológicos que se sincronizan internamente, lo que es importante para una óptima función. Las interrupciones circadianas sueño-vigilia y los desajustes circadianos crónicos que se observan con frecuencia en enfermedades psiquiátricas y neurodegenerativas pueden ser tratados con fototerapia. Los efectos favorables sobre la sincronización circadiana, la calidad del sueño, el ánimo y el rendimiento cognitivo dependen de la duración, intensidad y composición espectral de la exposición a la luz. La adaptación y optimización de las condiciones de luz interior pueden constituir una manera de mejorar el bienestar, el alerta y el rendimiento cognitivo, y a largo plazo producir beneficios para la salud.

Lumière et chronobiologie : conséquences pour la santé et la maladie

La lumière environnementale synchronise l'horloge biologique primaire des mammifères dans le noyau supraquiasmatic, ainsi que de nombreuses horloges périphériques dans les tissus et les cellules, au jour solaire de 24 h. La lumière est l'agent synchronisant le plus fort (zeitgeber) du système circadien, conservant donc la plupart des rythmes biologiques et psychologiques synchronisés en interne, ce qui est important pour un fonctionnement optimal. Les troubles circadiens veille-sommeil et le décalage circadien chronique, souvent observés dans les maladies psychiatriques et neurodégénératives, peuvent être traités par luminothérapie. L'effet bénéfique sur la synchronisation circadienne, la qualité du sommeil, l'humeur et la performance cognitive dépend de la chronologie, de l'intensité et de la composition spectrale de l'exposition à la lumière. Personnaliser et optimiser les conditions de lumière en intérieur pourraient permettre d'améliorer le bien-être, la vigilance et la performance cognitive et, à long terme, être bénéfique pour la santé.

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