Research abstracts of photobiological effects of sunlight in the eyes and brain

Photobiology: how does light affect human biology?

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Retinohypothalamic tract

A novel human opsin in the inner retina
Provencio, I., Rodriguez, I. R., Jiang, G., Hayes, W. P., Moreira, E. F., & Rollag, M. D. (2000).
The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 20(2), 600–605.

Here we report the identification of a novel human opsin, melanopsin, that is expressed in cells of the mammalian inner retina. The human melanopsin gene consists of 10 exons and is mapped to chromosome 10q22. This chromosomal localization and gene structure differs significantly from that of other human opsins that typically have four to seven exons. A survey of 26 anatomical sites indicates that, in humans, melanopsin is expressed only in the eye. In situ hybridization histochemistry shows that melanopsin expression is restricted to cells within the ganglion and amacrine cell layers of the primate and murine retinas. Notably, expression is not observed in retinal photoreceptor cells, the opsin-containing cells of the outer retina that initiate vision. The unique inner retinal localization of melanopsin suggests that it is not involved in image formation but rather may mediate nonvisual photoreceptive tasks, such as the regulation of circadian rhythms and the acute suppression of pineal melatonin. The anatomical distribution of melanopsin-positive retinal cells is similar to the pattern of cells known to project from the retina to the suprachiasmatic nuclei of the hypothalamus, a primary circadian pacemaker.

Phototransduction by Retinal Ganglion Cells That Set the Circadian Clock
Berson, D. M., Dunn, F. A., & Takao, M. (2002).
Science, 295(5557), 1070–1073.

Light synchronizes mammalian circadian rhythms with environmental time by modulating retinal input to the circadian pacemaker—the suprachiasmatic nucleus (SCN) of the hypothalamus. Such photic entrainment requires neither rods nor cones, the only known retinal photoreceptors. Here, we show that retinal ganglion cells innervating the SCN are intrinsically photosensitive. Unlike other ganglion cells, they depolarized in response to light even when all synaptic input from rods and cones was blocked. The sensitivity, spectral tuning, and slow kinetics of this light response matched those of the photic entrainment mechanism, suggesting that these ganglion cells may be the primary photoreceptors for this system.

Melanopsin-Containing Retinal Ganglion Cells: Architecture, Projections, and Intrinsic Photosensitivity.
Hattar, S., Liao, H. W., Takao, M., Berson, D. M., & Yau, K. W. (2002). *Science, 295(5557),* 1065–1070.

The primary circadian pacemaker, in the suprachiasmatic nucleus (SCN) of the mammalian brain, is photoentrained by light signals from the eyes through the retinohypothalamic tract. Retinal rod and cone cells are not required for photoentrainment. Recent evidence suggests that the entraining photoreceptors are retinal ganglion cells (RGCs) that project to the SCN. The visual pigment for this photoreceptor may be melanopsin, an opsin-like protein whose coding messenger RNA is found in a subset of mammalian RGCs. By cloning rat melanopsin and generating specific antibodies, we show that melanopsin is present in cell bodies, dendrites, and proximal axonal segments of a subset of rat RGCs. In mice heterozygous for tau-lacZ targeted to the melanopsin gene locus, β-galactosidase–positive RGC axons projected to the SCN and other brain nuclei involved in circadian photoentrainment or the pupillary light reflex. Rat RGCs that exhibited intrinsic photosensitivity invariably expressed melanopsin. Hence, melanopsin is most likely the visual pigment of phototransducing RGCs that set the circadian clock and initiate other non–image-forming visual functions.

Melanopsin-Expressing Retinal Ganglion-Cell Photoreceptors: Cellular Diversity and Role in Pattern Vision.
Ecker, J. L., Dumitrescu, O. N., Wong, K. Y., Alam, N. M., Chen, S.-K., LeGates, T., … Hattar, S. (2010). Melanopsin-Expressing Retinal Ganglion-Cell Photoreceptors: Cellular Diversity and Role in Pattern Vision.
Neuron, 67(1), 49–60.

Using the photopigment melanopsin, intrinsically photosensitive retinal ganglion cells (ipRGCs) respond directly to light to drive circadian clock resetting and pupillary constriction. We now report that ipRGCs are more abundant and diverse than previously appreciated, project more widely within the brain, and can support spatial visual perception. A Cre-based melanopsin reporter mouse line revealed at least five subtypes of ipRGCs with distinct morphological and physiological characteristics. Collectively, these cells project beyond the known brain targets of ipRGCs to heavily innervate the superior colliculus and dorsal lateral geniculate nucleus, retinotopically organized nuclei mediating object localization and discrimination. Mice lacking classical rod-cone photoreception, and thus entirely dependent on melanopsin for light detection, were able to discriminate grating stimuli from equiluminant gray and had measurable visual acuity. Thus, nonclassical retinal photoreception occurs within diverse cell types and influences circuits and functions encompassing luminance as well as spatial information.

Melanopsin and rod-cone photoreceptors play different roles in mediating pupillary light responses during exposure to continuous light in humans.
Gooley, J. J., Ho Mien, I., St Hilaire, M. A., Yeo, S.-C., Chua, E. C.-P., van Reen, E., … Lockley, S. W. (2012).
The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 32(41), 14242–14253.

In mammals, the pupillary light reflex is mediated by intrinsically photosensitive melanopsin-containing retinal ganglion cells that also receive input from rod–cone photoreceptors. To assess the relative contribution of melanopsin and rod–cone photoreceptors to the pupillary light reflex in humans, we compared pupillary light responses in normally sighted individuals (n = 24) with a blind individual lacking rod–cone function. Here, we show that visual photoreceptors are required for normal pupillary responses to continuous light exposure at low irradiance levels, and for sustained pupillary constriction during exposure to light in the long-wavelength portion of the visual spectrum. In the absence of rod–cone function, pupillomotor responses are slow and sustained, and cannot track intermittent light stimuli, suggesting that rods/cones are required for encoding fast modulations in light intensity. In sighted individuals, pupillary constriction decreased monotonically for at least 30 min during exposure to continuous low-irradiance light, indicating that steady-state pupillary responses are an order of magnitude slower than previously reported. Exposure to low-irradiance intermittent green light (543 nm; 0.1–4 Hz) for 30 min, which was given to activate cone photoreceptors repeatedly, elicited sustained pupillary constriction responses that were more than twice as great compared with exposure to continuous green light. Our findings demonstrate nonredundant roles for rod–cone photoreceptors and melanopsin in mediating pupillary responses to continuous light. Moreover, our results suggest that it might be possible to enhance nonvisual light responses to low-irradiance exposures by using intermittent light to activate cone photoreceptors repeatedly in humans.

Measuring and using light in the melanopsin age.
Lucas, R. J., Peirson, S. N., Berson, D. M., Brown, T. M., Cooper, H. M., Czeisler, C. A., … Brainard, G. C. (2014).
Neurosciences, 37(1), 1–9.

- Photoreceptive retinal ganglion cells (ipRGCs) regulate behavior and physiology.
- ipRGCs use melanopsin-dependent intrinsic light responses and rod/cone inputs.
- The relative contribution of each photoreceptor to evoked responses is not fully understood.
- A method for quantifying light is presented that accounts for complex photoreceptive inputs.
- Guidance for those designing architectural and therapeutic lighting is provided.

Light is a potent stimulus for regulating circadian, hormonal, and behavioral systems. In addition, light therapy is effective for certain affective disorders, sleep problems, and circadian rhythm disruption. These biological and behavioral effects of light are influenced by a distinct photoreceptor in the eye, melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs), in addition to conventional rods and cones. We summarize the neurophysiology of this newly described sensory pathway and consider implications for the measurement, production, and application of light. A new light-measurement strategy taking account of the complex photoreceptive inputs to these non-visual responses is proposed for use by researchers, and simple suggestions for artificial/architectural lighting are provided for regulatory authorities, lighting manufacturers, designers, and engineers.

Melanopsin: photoreceptors, physiology and potential
Palumaa T., Gilhooley M.J., Jagannath A., Hankins M.W.,Hughes S., Peirson S., (2018)
Physiology 5, 68-74

The discovery of melanopsin-expressing photosensitive retinal ganglion cells (pRGCs) has led to a fundamental change in our understanding of retinal light detection. pRGCs perform a broad range of non-visual functions —most notably mediating circadian entrainment to the environmental light/dark cycle. However, over the last two decades it has become clear that the melanopsin system is far more complex than first realised, influencing a wide range of physiology and behaviour, including pupillary constriction, light aversion, sleep, learning and memory and even mood. Here we provide an overview of the key areas of physiology known to be mediated by melanopsin pRGCs, as well as emerging translational opportunities.

Melanopsin contributions to non-visual and visual function
Spitschan M., (2019) *Behavioral Sciences,* 30, 67-72

Melanopsin is a short-wavelength-sensitive photopigment that was discovered only around 20 years ago. It is expressed in the cell bodies and processes of a subset of retinal ganglion cells in the retina (the intrinsically photosensitive retinal ganglion cells; ipRGCs), thereby allowing them to signal light even in the absence of cone and rod input. Many of the fundamental properties of melanopsin signalling in humans for both visual (e.g. detection, discrimination, brightness estimation) and non-visual function (e.g. melatonin suppression, circadian phase shifting) remain to be elucidated. Here, we give an overview of what we know about melanopsin contributions in visual function and non-visual function.

What is the 'spectral diet' of humans?
Webler F.S., Spitschan M., Foster R. G., Andersen M., Peirson S.N., (2019) Behavioral Sciences, 30, 80-86

Our visual perception of the world — seeing form and colour or navigating the environment — depends on the interaction of light and matter in the environment. Light also has a more fundamental role in regulating rhythms in physiology and behaviour, as well as in the acute secretion of hormones such as melatonin and changes in alertness, where light exposure at short-time, medium-time and long-time scales has different effects on these visual and non-visual functions. Yet patterns of light exposure in the real world are inherently messy: we move in and out of buildings and are therefore exposed to mixtures of artificial and natural light, and the physical makeup of our environment can also drastically alter the spectral composition and spatial distribution of the emitted light. In spatial vision, the examination of natural image statistics has proven to be an important driver in research. Here, we expand this concept to the spectral domain and develop the concept of the 'spectral diet' of humans.

Chronobiological processes

Circadian photoreception in the retinally degenerate mouse (rd/rd).
Foster RG1, Provencio I, Hudson D, Fiske S, De Grip W, Menaker M J Comp Physiol A. 1991 Jul;169(1):39-50.

We have examined the effects of light on circadian locomotor rhythms in retinally degenerate mice (C57BL/6J mice homozygous for the rd allele: rd/rd). The sensitivity of circadian photoreception in these mice was determined by varying the irradiance of a 15 min light pulse (515 nm) given at circadian time 16 and measuring the magnitude of the phase shift of the locomotor rhythm. Experiments were performed on animals 80 days of age. Despite the loss of visual photoreceptors in the rd/rd retina, animals showed circadian responses to light that were indistinguishable from mice with normal retinas (rd/+ and +/+). While no photoreceptor outersegments were identified in the retina of rd/rd animals (80-100 days of age), we did identify a small number of perikarya that were immunoreactive for cone opsins, and even fewer cells that contained rod opsin. Using HPLC, we demonstrated the presence and photoisomerization of the rhodopsin chromophore 11-cis retinaldehyde. The rd/rd retinas contained about 2% of 11-cis retinaldehyde found in +/+ retinas. We have yet to determine whether the opsin immunoreactive perikarya or some other unidentified cell type mediate circadian light detection in the rd/rd retina.

Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor
Brainard GC1, Hanifin JP, Greeson JM, Byrne B, Glickman G, Gerner E, Rollag MD.. J Neurosci. 2001 Aug 15;21(16):6405-12.

The photopigment in the human eye that transduces light for circadian and neuroendocrine regulation, is unknown. The aim of this study was to establish an action spectrum for light-induced melatonin suppression that could help elucidate the ocular photoreceptor system for regulating the human pineal gland. Subjects (37 females, 35 males, mean age of 24.5 +/- 0.3 years) were healthy and had normal color vision. Full-field, monochromatic light exposures took place between 2:00 and 3:30 A.M. while subjects' pupils were dilated. Blood samples collected before and after light exposures were quantified for melatonin. Each subject was tested with at least seven different irradiances of one wavelength with a minimum of 1 week between each nighttime exposure. Nighttime melatonin suppression tests (n = 627) were completed with wavelengths from 420 to 600 nm. The data were fit to eight univariant, sigmoidal fluence-response curves (R(2) = 0.81-0.95). The action spectrum constructed from these data fit an opsin template (R(2) = 0.91), which identifies 446-477 nm as the most potent wavelength region providing circadian input for regulating melatonin secretion. The results suggest that, in humans, a single photopigment may be primarily responsible for melatonin suppression, and its peak absorbance appears to be distinct from that of rod and cone cell photopigments for vision. The data also suggest that this new photopigment is retinaldehyde based. These findings suggest that there is a novel opsin photopigment in the human eye that mediates circadian photoreception.

An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans.
Thapan, K., Arendt, J., & Skene, D. J. (2001). *The Journal of Physiology,* 535(1), 261–267.

1. Non-image forming, irradiance-dependent responses mediated by the human eye include synchronisation of the circadian axis and suppression of pineal melatonin production. The retinal photopigment(s) transducing these light responses in humans have not been characterised. 2. Using the ability of light to suppress nocturnal melatonin production, we aimed to investigate its spectral sensitivity and produce an action spectrum. Melatonin suppression was quantified in 22 volunteers in 215 light exposure trials using monochromatic light (30 min pulse administered at circadian time (CT) 16-18) of different wavelengths (lambda(max) 424, 456, 472, 496, 520 and 548 nm) and irradiances (0.7-65.0 microW cm(-2)). 3. At each wavelength, suppression of plasma melatonin increased with increasing irradiance. Irradiance-response curves (IRCs) were fitted and the generated half-maximal responses (IR(50)) were corrected for lens filtering and used to construct an action spectrum. 4. The resulting action spectrum showed unique short-wavelength sensitivity very different from the classical scotopic and photopic visual systems. The lack of fit (r(2) < 0.1) of our action spectrum with the published rod and cone absorption spectra precluded these photoreceptors from having a major role. Cryptochromes 1 and 2 also had a poor fit to the data. Fitting a series of Dartnall nomograms generated for rhodopsin-based photopigments over the lambda(max) range 420-480 nm showed that rhodopsin templates between lambda(max) 457 and 462 nm fitted the data well (r(2) > or =0.73). Of these, the best fit was to the rhodopsin template with lambda(max) 459 nm (r(2) = 0.74). 5. Our data strongly support a primary role for a novel short-wavelength photopigment in light-induced melatonin suppression and provide the first direct evidence of a non-rod, non-cone photoreceptive system in humans.Abstract

Human circadian rhythms: physiological and therapeutic relevance of light and melatonin.
Skene DJ, Arendt J. Ann Clin Biochem. 2006 Sep;43(Pt 5):344-53.

Ocular light plays a key role in human physiology by transmitting time of day information. The production of the pineal gland hormone melatonin is under the control of the light-dark cycle. Its profile of secretion defines biological night and it has been called the 'darkness hormone'. Light mediates a number of non-visual responses, such as phase shifting the internal circadian clock, increasing alertness, heart rate and pupil constriction. Both exogenous melatonin and light, if appropriately

timed, can phase shift the human circadian system. These 'chronobiotic' effects of light and melatonin have been used successfully to alleviate and correct circadian rhythm disorders, such as those experienced following travel across time zones, in night shift work and in circadian sleep disorders. The effectiveness of melatonin and light are currently being optimized in terms of time of administration, light intensity, duration and wavelength, and melatonin dose and formulation. The aim of this review is not to replicate information that has been reported in a number of reviews of the human circadian timing system and the role of melatonin and light, but rather to extract findings relevant to the field of clinical biochemistry.

A circadian gene expression atlas in mammals: implications for biology and medicine.
Zhang, R., Lahens, N. F., Ballance, H. I., Hughes, M. E., & Hogenesch, J. B. (2014). *Proceedings of the National Academy of Sciences of the United States of America,* 111(45), 16219–16224.

To characterize the role of the circadian clock in mouse physiology and behavior, we used RNA-seq and DNA arrays to quantify the transcriptomes of 12 mouse organs over time. We found 43% of all protein coding genes showed circadian rhythms in transcription somewhere in the body, largely in an organ-specific manner. In most organs, we noticed the expression of many oscillating genes peaked during transcriptional "rush hours" preceding dawn and dusk. Looking at the genomic landscape of rhythmic genes, we saw that they clustered together, were longer, and had more spliceforms than nonoscillating genes. Systems-level analysis revealed intricate rhythmic orchestration of gene pathways throughout the body. We also found oscillations in the expression of more than 1,000 known and novel noncoding RNAs (ncRNAs). Supporting their potential role in mediating clock function, ncRNAs conserved between mouse and human showed rhythmic expression in similar proportions as protein coding genes. Importantly, we also found that the majority of best-selling drugs and World Health Organization essential medicines directly target the products of rhythmic genes. Many of these drugs have short half-lives and may benefit from timed dosage. In sum, this study highlights critical, systemic, and surprising roles of the mammalian circadian clock and provides a blueprint for advancement in chronotherapy.

Artificial Light at Night (ALAN) and breast cancer incidence worldwide: A revisit of earlier findings with analysis of current trends.
Rybnikova, N., Haim, A., & Portnov, B. A. (2015). *Chronobiology International,* 32(6), 757–773.

In a study published in Cancer Causes & Control in 2010, Kloog with co-authors tested, apparently for the first time, the association between population-level ambient exposure to artificial light at night (ALAN) and incidence of several cancers in women from 164 countries worldwide. The study was based on 1996–2002 data and concluded that breast cancer (BC) incidence was significantly and positively associated with ALAN, while no such association was revealed for other cancer types. An open question, however, remains whether the trends revealed by Kloog and co-authors were time specific or also hold true for more recent data. Using information obtained from the GLOBOCAN, US-DMSP and World Bank's 2002 and 2012 databases, we reanalyzed the strength of association between BC incidence rates in 180 countries worldwide and ALAN, controlling for several country-level predictors, including birth rates, percent of urban population, per capita GDP and electricity consumption. We also compared BC age-standardized rates (ASRs) with multi-annual ALAN measurements, considering potentially different latency periods. Compared with the results of Kloog et al.'s analysis of the year-2002 BC-data, the association between BC and ALAN appears to have weakened overall, becoming statistically insignificant in the year 2012 after being controlled for potential confounders ($t < 0.3$; $p > 0.5$). However, when the entire sample of countries was disaggregated into geographic clusters of similarly developed countries, a positive BC-ALAN association re-emerged as statistically significant ($t > 2.2$; $p < 0.01$), helping to explain, along with other factors covered by the analysis, about 65–85% of BC ASR variability worldwide, depending on the model type. Although the present analysis reconfirms a positive BC-ALAN association, this association appeared to diverge regionally in recent years, with countries in Western Europe showing the highest levels of such association, while countries in Southeast Asia and Gulf States exhibiting relatively low BC rates against the backdrop of relatively high ALAN levels. This regional stratification may be due to additional protective mechanisms, diminishing BC risks and potentially attributed to the local diet and lifestyles.

Effects of light on human circadian rhythms, sleep and mood.
Blume C., Garbazza C., Spitschan M., (2019) *Somnologie,* ,Vol. 23,147–156

Humans live in a 24-hour environment, in which light and darkness follow a diurnal pattern. Our circadian pacemaker, the suprachiasmatic nuclei (SCN) in the hypothalamus, is entrained to the 24-hour solar day via a pathway from the retina and synchronises our internal biological rhythms. Rhythmic variations in ambient illumination impact behaviours such as rest during sleep and activity during wakefulness as well as their underlying biological processes. Rather recently, the availability of artificial light has substantially changed the light environment, especially during evening and night hours. This may increase the risk of developing circadian rhythm sleep-wake disorders (CRSWD), which are often caused by a misalignment of endogenous circadian rhythms and external light-dark cycles. While the exact relationship between the availability of artificial light and CRSWD remains to be established, nocturnal light has been shown to alter circadian rhythms and sleep in humans. On the other hand, light can also be used as an effective and noninvasive therapeutic option with little to no side effects, to improve sleep, mood and general well-being. This article reviews our current state of knowledge regarding the effects of light on circadian rhythms, sleep, and mood.

Cognition, mood and sleep

Can light make us bright? Effects of light on cognition and sleep.
Chellappa SL, Gordijn MC, Cajochen C. Prog Brain Res. 2011;190:119-33.

Abstract
Light elicits robust nonvisual effects on numerous physiological and behavioral variables, such as the human sleep-wake cycle and cognitive performance. Light effects crucially rely on properties such as dose, duration, timing, and wavelength. Recently, the use of methods such as fMRI to assess light effects on nonvisual brain responses has revealed how light can optimize brain function during specific cognitive tasks, especially in tasks of sustained attention. In this chapter, we address two main issues: how light impinges on cognition via consolidation of human sleep-wake cycles; and how light directly impacts on sleep and cognition, in particular in tasks of sustained attention. A thorough understanding of how light affects sleep and cognitive performance may help to improve light settings at home and at the workplace in order to improve well-being.

Light as a modulator of cognitive brain function.
Vandewalle G1, Maquet P, Dijk DJ. Trends Cogn Sci. 2009 Oct;13(10):429-38.

Humans are a diurnal species usually exposed to light while engaged in cognitive tasks. Light not only guides performance on these tasks through vision but also exerts non-visual effects that are mediated in part by recently discovered retinal ganglion cells maximally sensitive to blue light. We review recent neuroimaging studies which demonstrate that the wavelength, duration and intensity of light exposure modulate brain responses to (non-visual) cognitive tasks. These responses to light are initially observed in alertness-related subcortical structures (hypothalamus, brainstem, thalamus) and limbic areas (amygdala and hippocampus), followed by modulations of activity in cortical areas, which can ultimately affect behaviour. Light emerges as an important modulator of brain function and cognition.

The stimulating impact of light on brain cognition function.
Vandewalle G. Med Sci (Paris). 2014 Oct;30(10):902-9.

Light regulates multiple non-visual circadian, neuroendocrine, and neurobehavioral functions, and conveys a strong stimulating signal for alert-ness and cognition. This review summarizes a series of neuroimaging studies investigating the brain mechanisms underlying the latter stimulating impact of light. Results of these studies are compatible with a scenario where light would first hit

subcortical areas involved in arousal regulation before affecting cortical areas involved in the ongoing non-visual cognitive process, and then cognitive performance. Recent data demonstrated that the non-visual impact of light is most likely triggered via outputs from intrinsically photosensitive retinal ganglion cells (ipRGC) expressing the photopigment melanopsin, which are maximally sensitive to blue light. In addition, the stimulating impact of light is intimately related to wakefulness regulation as it changes with circadian phase and sleep pressure. Finally, markers of inter-individual difference have also been described: age, PERIOD3 genotype, and psychiatric status. This review emphasizes the importance of light for human brain cognitive function and for cognition in general.

Non-circadian direct effects of light on sleep and alertness: lessons from transgenic mouse models.
Hubbard J, Ruppert E, Gropp CM, Bourgin P. Sleep Med Rev. 2013 Dec;17(6):445-52.

Light exerts a strong non-visual influence on human physiology and behavior. Additionally light is known to affect sleep indirectly through the phase shifting of circadian rhythms, and directly, promoting alertness in humans and sleep in nocturnal species. Little attention has been paid to the direct non-image-forming influence of light until recently with the discovery and emerging knowledge on melanopsin, a photopigment which is maximally sensitive to the blue spectrum of light and expressed in a subset of intrinsically photosensitive retinal ganglion cells. Indeed, the development of transgenic mouse models targeting different phototransduction pathways has allowed researchers to decipher the mechanisms by which mammals adapt sleep to their light environment. This review summarizes the novel concepts and discrepancies from recent publications relating to the non-circadian effects of light on sleep and waking. Specifically, we discuss whether darkness, in addition to light, affects their quality. Furthermore, we seek to understand whether longer sustained periods of light exposure can influence sleep, if the direct photic regulation depends on time of day, and whether this affects the homeostatic sleep process. Moreover, the neural pathways by which light exerts a direct influence on sleep will be discussed including the respective role of rods/cones and melanopsin. Finally, we suggest that light weighs on the components of the flip-flop switch model to induce respectively sleep or waking, in nocturnal and diurnal animals. Taking these data into account we therefore propose a novel model of sleep regulation based on three processes; the direct photic regulation interacting with the circadian and homeostatic drives to determine the timing and quality of sleep and waking. An outlook of promising clinical and non-clinical applications of these findings will be considered as well as directions for future animal and human research.

Complex interaction of circadian and non-circadian effects of light on mood: shedding new light on an old story.
Stephenson KM, Schroder CM, Bertschy G, Bourgin P. Sleep Med Rev. 2012 Oct;16(5):445-54

In addition to its role in vision, light exerts strong effects on behavior. Its powerful role in the modulation of mood is well established, yet remains poorly understood. Much research has focused on the effects of light on circadian rhythms and subsequent interaction with alertness and depression. The recent discovery of a third photoreceptor, melanopsin, expressed in a subset of retinal ganglion cells, allows major improvement of our understanding of how photic information is processed. Light affects behavior in two ways, either indirectly through the circadian timing system, or directly through mechanisms that are independent of the circadian system. These latter effects have barely been studied in regard to mood, but recent investigations on the direct effects of light on sleep and alertness suggest additional pathways through which light could influence mood. Based on our recent findings, we suggest that light, via melanopsin, may exert its antidepressant effect through a modulation of the homeostatic process of sleep. Further research is needed to understand how these mechanisms interplay and how they contribute to the photic regulation of mood. Such research could improve therapeutic management of affective disorders and influence the management of societal lighting conditions.

Light-sensitive brain pathways and aging.
Daneault V, Dumont M, Massé É, Vandewalle G, Carrier J., J Physiol Anthropol. 2016 Mar

Notwithstanding its effects on the classical visual system allowing image formation, light acts upon several non-image-forming (NIF) functions including body temperature, hormonal secretions, sleep-wake cycle, alertness, and cognitive performance. Studies have shown that NIF functions are maximally sensitive to blue wavelengths (460-480 nm), in comparison to longer light wavelengths. Higher blue light sensitivity has been reported for melatonin suppression, pupillary constriction, vigilance, and performance improvement but also for modulation of cognitive brain functions. Studies investigating acute stimulating effects of light on brain activity during the execution of cognitive tasks have suggested that brain activations progress from subcortical regions involved in alertness, such as the thalamus, the hypothalamus, and the brainstem, before reaching cortical regions associated with the ongoing task. In the course of aging, lower blue light sensitivity of some NIF functions has been reported. Here, we first describe neural pathways underlying effects of light on NIF functions and we discuss eye and cerebral mechanisms associated with aging which may affect NIF light sensitivity. Thereafter, we report results of investigations on pupillary constriction and cognitive brain sensitivity to light in the course of aging. Whereas the impact of light on cognitive brain responses appears to decrease substantially, pupillary constriction seems to remain more intact over the lifespan. Altogether, these results demonstrate that aging research should take into account the diversity of the pathways underlying the effects of light on specific NIF functions which may explain their differences in light sensitivity.

Insight into the Role of Photoreception and Light Intervention for Sleep and Neuropsychiatric Behaviour in the Elderly.
Wulff K, Foster RG., Curr Alzheimer Res.

Light exerts influences on many physiological and behavioural functions in humans. These functions can be described as image-forming (IF) and non-image forming (NIF) visual processes, both originating in the retina of the eye. Image-forming refers to vision; the process of detecting and distinguishing shapes and colour of objects. Non-image forming refers to detecting level of light intensity or brightness of ambient space, which affects basal physiology such as cycles of rest and activity or the endocrine system. Rod and cone photoreceptors in the outer retinal layer are most important for image-forming vision, while non-image forming functions depend upon additional input from the photopigment melanopsin, which is expressed in retinal ganglion cells (RGC) that makes these cells photosensitive (pRGC). Projections of these pRGCs convey light-induced electrical impulses to a number of brain regions. Visual acuity and colour contrast naturally diminishes with age but dementia often has major effects on the visual processing systems, which impact on the quality of life. The ability of humans to manipulate their light exposure has the immediate potential to either create problems with human physiology (as in shift workers) or to compensate physiological disadvantages (of IF and NIF visual impairment). This mini-review describes the impact of aging on the function of the eye with respect to nonimage forming effects of light, summarises light intervention studies for sleep and neuropsychiatric symptoms and considers implications from photoreceptor-weighted light intensities for biologically effective light intervention and lighting solutions for patients with dementia.

Daytime light exposure dynamically enhances brain responses.
Vandewalle G, Balteau E, Phillips C, Degueldre C, Moreau V, Sterpenich V, Albouy G, Darsaud A, Desseilles M, Dang-Vu TT, Peigneux P, Luxen A, Dijk DJ, Maquet P. Curr Biol. 2006 Aug 22;16(16):1616-21.

In humans, light enhances both alertness and performance during nighttime and daytime [1-4] and influences regional brain function [5]. These effects do not correspond to classical visual responses but involve a non-image forming (NIF) system, which elicits greater endocrine, physiological, neurophysiological, and behavioral responses to shorter light wavelengths than to wavelengths geared toward the visual system [6-11]. During daytime, the neural changes induced by light exposure, and their time courses, are largely unknown. With functional magnetic resonance imaging (fMRI), we characterized the neural correlates of the alerting effect of daytime light by assessing the responses to an auditory oddball task [12-15], before and after a short exposure to a bright white light. Light-induced improve-

ment in subjective alertness was linearly related to responses in the posterior thalamus. In addition, light enhanced responses in a set of cortical areas supporting attentional oddball effects, and it prevented decreases of activity otherwise observed during continuous darkness. Responses to light were remarkably dynamic. They declined within minutes after the end of the light stimulus, following various region-specific time courses. These findings suggest that light can modulate activity of subcortical structures involved in alertness, thereby dynamically promoting cortical activity in networks involved in ongoing nonvisual cognitive processes.

Light, Alertness, and Alerting Effects of White Light: A Literature Overview.
Lok R, Smolders KCHJ, Beersma DGM, de Kort YAW. J Biol Rhythms. 2018 Dec;33(6):589-601.

Light is known to elicit non-image-forming responses, such as effects on alertness. This has been reported especially during light exposure at night. Nighttime results might not be translatable to the day. This article aims to provide an overview of (1) neural mechanisms regulating alertness, (2) ways of measuring and quantifying alertness, and (3) the current literature specifically regarding effects of different intensities of white light on various measures and correlates of alertness during the daytime. In general, the present literature provides inconclusive results on alerting effects of the intensity of white light during daytime, particularly for objective measures and correlates of alertness. However, the various research paradigms employed in earlier studies differed substantially, and most studies tested only a limited set of lighting conditions. Therefore, the alerting potential of exposure to more intense white light should be investigated in a systematic, dose-dependent manner with multiple correlates of alertness and within one experimental paradigm over the course of day.

Acute alerting effects of light: A systematic literature review.
Souman JL, Tinga AM, Te Pas SF, van Ee R, Vlaskamp BNS. Behav Brain Res. 2018 Jan 30;337:228-239.

Periodic, well timed exposure to light is important for our health and wellbeing. Light, in particular in the blue part of the spectrum, is thought to affect alertness both indirectly, by modifying circadian rhythms, and directly, giving rise to acute effects. We performed a systematic review of empirical studies on direct, acute effects of light on alertness to evaluate the reliability of these effects. In total, we identified 68 studies in which either light intensity, spectral distribution, or both were manipulated, and evaluated the effects on behavioral measures of alertness, either subjectively or measured in reaction time performance tasks. The results show that increasing the intensity of polychromatic white light has been found to increase subjective ratings of alertness in a majority of studies, though a substantial proportion of studies failed to find significant effects, possibly due to small sample sizes or high baseline light intensities. The effect of the color temperature of white light on subjective alertness is less clear. Some studies found increased alertness with higher color temperatures, but other studies reported no detrimental effects of filtering out the short wavelengths from the spectrum. Similarly, studies that used monochromatic light exposure showed no systematic pattern for the effects of blue light compared to longer wavelengths. Far fewer studies investigated the effects of light intensity or spectrum on alertness as measured with reaction time tasks and of those, very few reported significant effects. In general, the small sample sizes used in studies on acute alerting effects of light make it difficult to draw definitive conclusions and better powered studies are needed, especially studies that allow for the construction of dose-response curves.

Revisiting the alerting effect of light: A systematic review.
Xu Q, Lang CP. Sleep Med Rev. 2018 Oct;41:39-49.

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 were examined with reference to the three-process model. The post-illuminance alerting effect was examined separately due to its potential to offer flexible workplace-based light interventions to increase or maintain employees' alertness.

What keeps us awake? The role of clocks and hourglasses, light, and melatonin.
Cajochen C1, Chellappa S, Schmidt C. Int Rev Neurobiol. 2010;93:57-90

What is it that keeps us awake? Our assumption is that we consciously control our daily activities including sleep-wake behavior, as indicated by our need to make use of an alarm clock to wake up in the morning in order to be at work on time. However, when we travel across multiple time zones or do shift work, we realize that our intentionally planned timings to rest and to remain active can interfere with an intrinsic regulation of sleep/wake cycles. This regulation is driven by a small region in the anterior hypothalamus of the brain, termed as the "circadian clock". This clock spontaneously synchronizes with the environmental light-dark cycle, thus enabling all organisms to adapt to and anticipate environmental changes. As a result, the circadian clock actively gates sleep and wakefulness to occur in synchrony with the light-dark cycles. Indeed, our internal clock is our best morning alarm clock, since it shuts off melatonin production and boosts cortisol secretion and heart rate 2-3h prior awakening from Morpheus arms. The main reason most of us still use artificial alarm clocks is that we habitually carry on a sleep depth and/or the sleep-wake timing is not ideally matched with our social/work schedule. This in turn can lead hourglass processes, as indexed by accumulated homeostatic sleep need over time, to strongly oppose the clock. To add to the complexity of our sleep and wakefulness behavior, light levels as well as exogenous melatonin can impinge on the clock, by means of their so-called zeitgeber (synchronizer) role or by acutely promoting sleep or wakefulness. Here we attempt to bring a holistic view on how light, melatonin, and the brain circuitry underlying circadian and homeostatic processes can modulate sleep and in particular alertness, by actively promoting awakening/arousal and sleep at certain times during the 24-h day.

Neural bases of the non-conscious perception of emotional signals
Tamietto, M., & de Gelder, B. (2010).. *Nature Reviews. Neuroscience,* 11(10), 697–709.

Many emotional stimuli are processed without being consciously perceived. Recent evidence indicates that subcortical structures have a substantial role in this processing. These structures are part of a phylogenetically ancient pathway that has specific functional properties and that interacts with cortical processes. There is now increasing evidence that non-consciously perceived emotional stimuli induce distinct neurophysiological changes and influence behaviour towards the consciously perceived world. Understanding the neural bases of the non-conscious perception of emotional signals will clarify the phylogenetic continuity of emotion systems across species and the integration of cortical and subcortical activity in the human brain.