Light as a central modulator of circadian rhythms, sleep and affect

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Abstract | Light has profoundly influenced the evolution of life on earth. As widely appreciated, light enables us to generate images of our environment. However, light — through intrinsically photosensitive retinal ganglion cells (ipRGCs) — also influences behaviours that are essential for our health and quality of life but are independent of image formation. These include the synchronization of the circadian clock to the solar day, tracking of seasonal changes and the regulation of sleep. Irregular light environments lead to problems in circadian rhythms and sleep, which eventually cause mood and learning deficits. Recently, it was found that irregular light can also directly affect mood and learning without producing major disruptions in circadian rhythms and sleep. In this Review, we discuss the indirect and direct influence of light on mood and learning, and provide a model for how light, the circadian clock and sleep interact to influence mood and cognitive functions.

Non-image-forming visual functions
(NIF visual functions). Light mediated-behaviours that are not involved in detecting contrasts, colour or motion of the visual scene. These include circadian photoentrainment and sleep regulation.

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The retina, which is located in the back of the eye, detects light for the formation of images and for object tracking[1]. However, our eyes are also essential for light detection for the regulation of several behavioural and physiological functions that are independent of image formation, which are collectively termed non-image-forming visual functions (NIF visual functions). These NIF functions include the adjustment of the internal circadian clock to light (circadian photoentrainment) and alterations in sleep and alertness. Therefore, light is essential for both image-forming and NIF functions.

The rotation of the earth about its axis results in periodic changes in the light–dark environment. This predictable change in the light environment enables organisms to confine their activity–rest rhythms and physiology to specific times of the day–night cycle. To anticipate changes in the light–dark environment, organisms have evolved an internal biological clock that runs with a period close to 24 hours in the absence of environmental influences such as light[2]. The circadian clock drives many outputs, which include the sleep–wake and metabolic cycles as well as hormonal changes. Proper alignment between light, the circadian clock and output behaviours produces a temporal order in organisms that is essential for survival[3].

The circadian clock partitions sleep to occur at a particular time of the day–night cycle, whereas a homeostatic mechanism tracks sleep need. This homeostatic drive accumulates during periods of wakefulness and diminishes with sleep. The combination of circadian mechanisms and homeostatic sleep drive determines the length of sleep[4]. It was assumed for many years that light influences sleep only secondarily through changes in circadian photoentrainment. However, several studies have now demonstrated that light directly affects both sleep onset and homeostatic sleep drive[5–9]. In this way, light, the circadian clock and sleep may closely interact to enable organisms to adapt to their environments.

This interaction may explain why changes in the light environment, such as those associated with shift work, shortened day lengths in winter and transmeridian travel, are associated with general changes in health, including mental health issues such as seasonal affective disorder (SAD), depression and cognitive dysfunction[10]. The effects of light on the circadian system have been thoroughly studied, with a focus on how changes in the light environment lead to changes in circadian rhythms that, in turn, influence sleep and contribute to alterations in mood and cognitive function. We refer to this as the indirect pathway by which changes in the light environment lead to mood and cognitive alterations.

In addition to the indirect pathway, several new findings show that light can also have direct effects on mood and cognition. Aberrant light stimulation can lead to mood and cognitive deficits independently of circadian arrhythmicity or sleep deprivation. We refer to this as the direct pathway by which light leads to changes in mood and cognition. Therefore, in addition to the

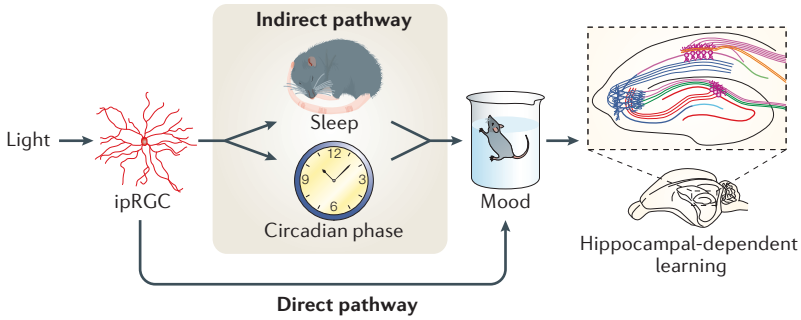

Figure 1 | **Model of the direct and indirect influences of light on mood and cognition.** Light can regulate mood and learning by first modulating sleep and circadian rhythms (indirect pathway), or it can directly affect mood without disrupting sleep or causing circadian arrhythmicity (direct pathway). These pathways have also been shown to mediate the effects of light on hippocampal-dependent learning in rodents. The effects of light on circadian rhythms, sleep and mood are mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs). Figure from REF. 85, Nature Publishing Group.

interdependence between light, circadian rhythms and sleep, affect now emerges as an additional function that is influenced by these three factors (FIG. 1).

In this Review, we discuss recent studies that have investigated the influence of light on mood regulation through these two pathways. We highlight studies in humans and rodent models that have led to advancements in our understanding of the retinal and brain circuits that are involved in these pathways. Last, we discuss the implications of these findings and consider how they can be applied to future investigations of the mechanisms underlying mood disorders and to the design of improved treatments for these disorders.

Mammalian light detection machinery

The solar day synchronizes circadian rhythms and sleep–wake cycles in animals and limits animals' activity to the correct temporal niche. Under normal conditions, organisms experience a 24-hour pattern of light–dark, and the circadian system of most animals uses the day-to-night transitions to align to environmental time. In non-mammalian vertebrates, extraocular photoreceptors, in addition to the eyes, detect light for circadian photoentrainment as well as other NIF functions[11]. In mammals, however, the eye is the only organ that is capable of detecting light for NIF functions[12], indicating that the extraocular photoreception that is observed in non-mammalian vertebrates is centralized to the eyes in mammals.

At the back of the eye, the retina contains the classical photoreceptors, rods and cones, which transform photon energy into an electrical signal[1]. This information is then conveyed to the brain through retinal ganglion cells (RGCs), the output neurons of the retina[13] (FIG. 2a). A mere decade or so ago, rods and cones were considered to be the only photoreceptive cells in the mammalian retina. However, an early study that characterized the spectral sensitivity of the circadian system provided the initial evidence for an additional photoreceptive system in the retina[14]. This finding was supported by the intriguing discovery that a group of blind humans who were unable to form images could nonetheless detect light for the regulation of melatonin secretion[15]. The evidence for the presence of an additional photoreceptive system was strengthened when genetically modified mice lacking rods and cones were likewise able to detect light for circadian photoentrainment as well as other NIF functions[16]. Together, these studies suggested that a non-rod and non-cone photoreceptor in the mammalian eye is important for mediating non-image responses to light. The discovery that the photopigment melanopsin is present in only a small minority of RGCs in rodents (initially thought to amount to 1–2% of total RGCs) suggested that this subset of RGCs might be the elusive third class of photoreceptor[17]. These melanopsin-expressing RGCs were shown to respond to light intrinsically in the absence of rod and/or cone signalling and so they were called intrinsically photosensitive RGCs (ipRGCs). However, like all ganglion cells, ipRGCs also receive light information secondarily from rods and cones[18–21]. Therefore, ipRGCs can detect light on their own through melanopsin and can also mediate rod and/or cone input (BOX 1).

Initially, ipRGCs were thought to constitute a uniform population whose predominant role is to influence circadian rhythms, as they project to the suprachiasmatic nucleus (SCN), the central circadian pacemaker. However, in depth investigations have revealed the existence of at least five subtypes of ipRGCs with different morphological and electrophysiological properties in rodents[22–29]. Together, these constitute 4–5% of the total number of RGCs[30] (FIG. 2a). In addition to their projections to the SCN, ipRGCs show widespread projection patterns throughout the rodent brain, targeting regions such as the subparaventricular zone and intergeniculate leaflet, which are important for the regulation of circadian rhythms; the ventrolateral preoptic area (VLPO) and lateral hypothalamus, which are important for the regulation of sleep; and the medial amygdala and lateral habenula, which have been implicated in mood regulation[30] (FIG. 2b). Therefore, ipRGCs emerge as leading candidates for mediating the effects of light on several behaviours such as circadian rhythms, sleep, alertness and mood.

The SCN, as a circadian pacemaker, drives rhythms in several downstream targets, which include brain regions that are implicated in sleep regulation, such as the VLPO and the lateral hypothalamus[31–38], and mood and motivational states, such as the locus coeruleus, amygdala, lateral habenula and ventral tegmental area[39–41] (FIG. 2). It is of interest that some brain targets receive input from both ipRGCs and the SCN[42–47] (FIG. 2c). This means that light can influence these areas through direct projections from ipRGCs but also that the SCN, in addition to its pacemaker function, can possibly function as a conduit for light input to these areas (FIG. 2). Therefore, the convergence of environmental light information directly from ipRGCs and indirectly through the SCN at specific times of the circadian cycle may influence the physiological functions of these brain regions, such as inducing sleep or influencing mood.

Circadian photoentrainment
The synchronization of internal circadian rhythms with the solar cycle. This renders circadian rhythms physiologically relevant.

Sleep drive
The pressure to sleep. Sleep drive is driven by homeostatic and circadian mechanisms that interact to determine its strength. The higher the sleep drive, the easier it is to fall asleep.

Shift work
A work schedule that varies irrespective of the solar day–night cycles. This type of work causes sleep and circadian problems and induces major health issues.

Seasonal affective disorder
(SAD). A seasonal form of depression that occurs as a manifestation of the shorter day length of the winter months.

Circadian rhythms
Internally generated near 24-hour rhythms in biological processes that are expressed in almost all tissues throughout the body.

Suprachiasmatic nucleus
(SCN). A brain region located in the hypothalamus that houses the central circadian pacemaker. The SCN synchronizes peripheral rhythms with the solar cycle.

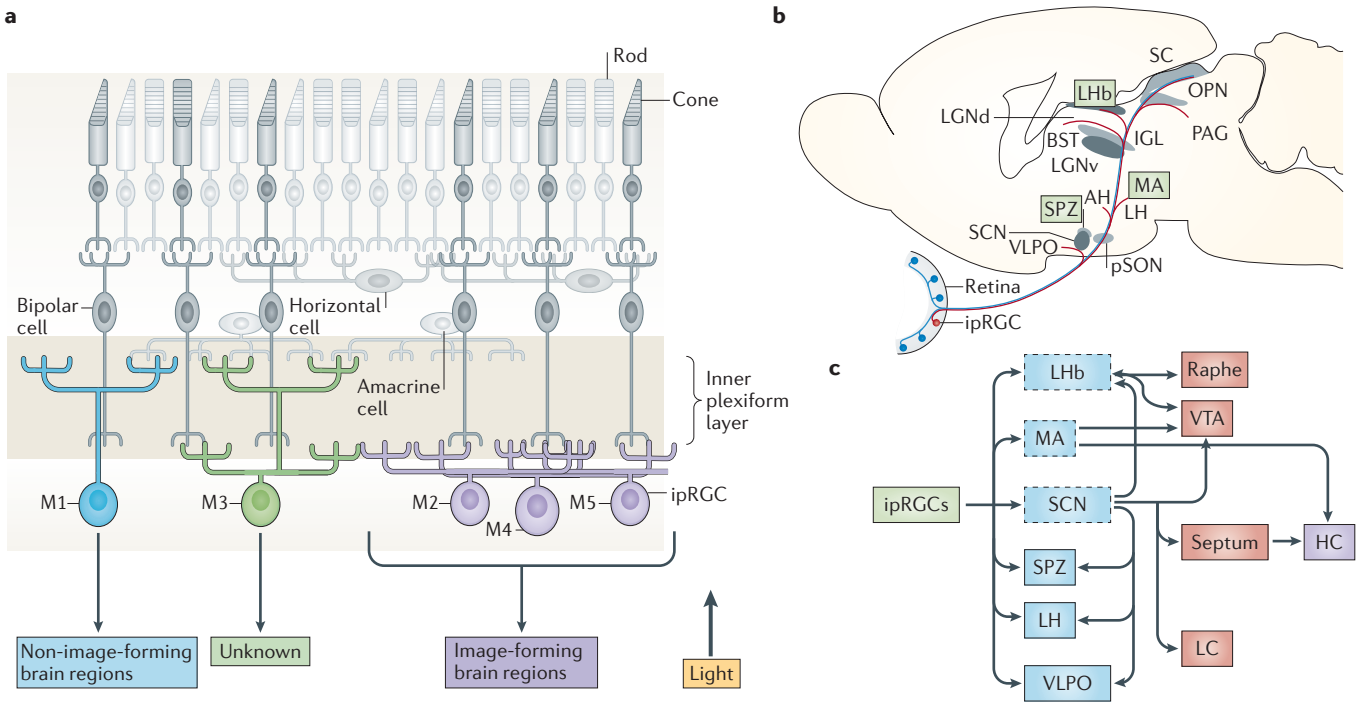

Figure 2 | **Retinal and brain circuits underlying the effects of light on non-image-forming visual functions.** **a** | A schematic view of the retina showing the organization of different neuronal populations and their synaptic connections. Rods and cones are confined to the photoreceptor layer. Light detected by rods and cones is processed and signalled to retinal ganglion cells (RGCs) through horizontal, amacrine and bipolar cells. RGCs are the only output neurons from the retina to the brain. A subset of RGCs (4–5% of the total number of RCGs) are intrinsically photosensitive RGCs (ipRGCs). There are at least five subtypes of ipRGCs (M1–M5) with different morphological and electrophysiological properties, which show widespread projection patterns throughout the brain. **b** | ipRGCs project to numerous brain regions, including many that have a role in driving light-mediated behaviours, including circadian photoentrainment and sleep. In addition, ipRGCs also innervate nuclei involved in depression and/or anxiety, such as the medial amygdala (MA), lateral habenula (LHb) and subparaventricular zone (SPZ) (which are highlighted in green), indicating a possible direct role of light on mood. **c** | Several of the ipRGC targets, including the SPZ, ventrolateral preoptic area (VLPO), lateral hypothalamus (LH) and LHb, also receive innervation from the suprachiasmatic nucleus (SCN), raising the possibility that in addition to its pacemaker function, the SCN can also act as a conduit for light information. Interestingly, the MA and the LHb are also brain peripheral clocks (central and peripheral clocks are indicated by dashed lines) that receive direct retinal innervation. Areas involved in mood regulation (the ventral tegmental area (VTA) and raphe) and cognition (the hippocampus (HC)) can be influenced by light either through the SCN or in parallel through the MA and LHb. AH, anterior hypothalamus; BST, bed nucleus of the stria terminalis; IGL, intergeniculate leaflet; LC, locus coeruleus; LGNd, dorsal lateral geniculate nucleus; LGNv, ventral lateral geniculate nucleus; OPN, olivary pretectal nucleus; PAG, periaqueductal grey; pSON, supraoptic nucleus; SC, superior colliculus. Part **a** adapted with permission from REF. 30, Elsevier. Part **b** adapted with permission from REF. 131, Wiley.

The indirect pathway

The involvement of sleep and circadian rhythms in the aetiology of mood disorders is supported by well-documented alterations in sleep in patients with psychological alterations. Most patients with depression note poor quality of sleep, which begins to appear weeks before the recurrence of depression symptoms[48]. This is generally characterized by a disruption in sleep continuity.

Sleep can be divided into rapid eye movement sleep (REM sleep; also known as paradoxical sleep) and non-REM sleep. Non-REM sleep is further divided into several stages that are termed N1–N3, of which N3 is the stage during which slow-wave sleep (that is, deep sleep) occurs[49]. As described above, sleep timing, depth and duration are regulated by homeostatic and circadian factors[4]. Proper alignment between the circadian and homeostatic mechanisms improves the quality of sleep. Sleep recordings in patients with depression show a marked decrease in slow-wave sleep, decreased latency to REM sleep and an increase in the density of REM bouts[50]. In bipolar disorder, in which patients fluctuate between mania and depression, a striking reduction in the duration of sleep precedes the recurrence of a manic episode, and a primary characteristic of the manic state is a decrease in sleep need[51]. In addition to sleep disturbances, disruption of other circadian rhythms, such as alterations in daily rhythmic fluctuations of hormones (including melatonin and cortisol), is also evident in mood disorders[52–54].

As light has profound effects on circadian rhythms and sleep, research in the field has focused on the changes in circadian rhythms and sleep that occur as a result of altered light environments and their involvement in the induction of mood disorders. This has led

Box 1 | **Intrinsically photosensitive retinal ganglion cells**

Retinal photoreceptors transduce light energy into electrical signals that initiate vision. The classical photoreceptors, rods and cones, possess modified cilia that consist of stacks of membranes in which photopigments (rhodopsin and cone opsins) are concentrated. Rods are exquisitely sensitive and are able to detect even a few photons. Rods are therefore used for night vision. Cones are less sensitive than rods and are used for day and colour vision. Colour vision is mediated by cone photoreceptors that express cone opsins, which show sensitivity peaks at different wavelengths (colours) of light. Humans have three cone types: short wavelength-, mid-wavelength- and long wavelength-sensitive cones (for simplicity, we will refer to these as blue, green and red cones, respectively). Rods and cones relay photic information through multisynaptic pathways to retinal ganglion cells (RGCs), which innervate different areas in the brain for complex visual processing[13].

A surprising discovery showed that a subpopulation of RGCs are intrinsically photosensitive and express the photopigment melanopsin. These cells were thus termed ipRGCs[17–19]. The gene encoding melanopsin, *opn4*, was originally cloned from *Xenopus laevis* dermal melanophores and was shown to have orthologues in many mammalian species, including humans[141]. Sequence analysis shows that melanopsin shares more homology with invertebrate opsins than with vertebrate opsins, suggesting that melanopsin may use a different mechanism for light signalling than that used by the photopigments present in the rods and cones of vertebrates[142]. As ipRGCs do not have modified membranes in which the photopigment can be concentrated, melanopsin is expressed uniformly throughout the soma, dendrites and the initial segment of the axon[143]. The lack of membrane specialization makes ipRGCs less sensitive to light than rods and cones. However, ipRGCs are able to incorporate light signals over an extended period of time, resulting in an increase in their sensitivity during prolonged light stimulation. ipRGCs are most sensitive to wavelengths of light that are in the blue region of the light spectrum[144,145]. As ganglion cells, ipRGCs also convey light information from rods and cones in addition to their intrinsic melanopsin-dependent pathway and can control a range of light-mediated behaviours[30].

Originally, ipRGCs were thought to constitute a uniform population; however, recent discoveries have revealed that ipRGCs are highly diverse, comprising at least five distinct subtypes (M1–M5) in rodents based on morphological and electrophysiological analyses[22–29]. The originally identified population are now known as M1 ipRGCs and project predominantly to brain regions that are involved in non-image-forming visual functions, whereas the non-M1 ipRGCs show widespread projections to areas in the brain that are important for image formation. Subtypes of ipRGCs express varying levels of melanopsin and have different patterns of dendrite stratification in the inner plexiform layer[27,28,146,147], indicating that each subtype could have a particular role in detecting light intrinsically and in signalling rod and cone information to the brain.

to a model in which mood and cognitive disorders associated with changes in light exposure are caused by disruptions in circadian rhythms and sleep, essentially suggesting that the effects of light on mood and cognitive functions are secondary. In line with this hypothesis, several mood-related changes occur under different light environments in humans.

Seasonal changes in day length. SAD is a form of depression in which the onset of symptoms is coincident with decreasing day length during autumn and winter months[55]. The prevalence of SAD is greater in populations living at higher latitudes, where the seasonal changes in day length are more extreme[55]. Two major hypotheses have been put forth to explain this seasonal form of depression: alterations in the daily rhythms of melatonin release and circadian phase shift. Melatonin is a hormone that is released by the pineal gland. In humans, this release increases at night coincident with the onset of sleep and is thought to be an important factor in circadian and sleep regulation[56]. The presentation of light at night, which increases alertness, suppresses melatonin release in humans[57–60]. Studies have found altered melatonin rhythms in patients with SAD. However, there is also evidence that melatonin rhythms vary seasonally in healthy individuals, suggesting that further investigation of the possible role of melatonin in SAD is required[54,61,62]. Furthermore, the fact that melatonin release is also directly affected by light and that retinal sensitivity changes in SAD[63] suggest that it will be important to re-evaluate whether the depression occurs secondarily to changes in sleep or is a direct manifestation of reduced total light levels owing to the shorter day length.

According to the circadian phase shift hypothesis, sunrise occurring later during the winter months causes a delay in circadian rhythmicity[64,65]. This is thought to lead to a dissociation between sleep–wake cycles and other peripheral circadian rhythms that are more tightly coupled to the central circadian oscillator. Strong support for this delayed phase shift hypothesis lies in the antidepressant effects of morning exposure to bright light, which causes an advance in the phase of the clock[64–67]. Although phase delays have been observed in most patients with SAD, a minority of these patients show phase advances, indicating that they should respond better to evening light treatment. Indeed, some studies have shown that evening light treatment is as effective as an antidepressant as morning treatment[68–70]. Thus, there are perhaps two groups of patients with SAD — phase advanced and phase delayed — that would benefit from light treatment at different times of the day[71,72].

Seasonal mood changes are not restricted to SAD. In fact, seasonal fluctuations in mood have been observed in many patients with bipolar disorder. A profound switch in mood between periods of mania and depression characterizes bipolar disorder[73]. These mood swings can happen very quickly, and the triggers for these changes are largely unknown. However, shifts to the depressive phase have been observed to begin in autumn as day length decreases and often persist throughout the winter[74,75]. By March, when day length begins to increase in the northern hemisphere, manic episodes become more prevalent, a phenomenon nicknamed 'March madness' (REFS 74,76,77). The explanation for these seasonal changes is similar to that suggested for SAD. Strong support for this explanation lies in bright light treatments, which have therapeutic effects in patients with bipolar disorder who experience seasonal fluctuations[78]. In addition, bright light treatment can have a mania-inducing effect, providing further support for the influence of light on mood[79,80].

Transmeridian travel. Many individuals have experienced the general malaise, including poor mood and cognitive impairments, that is associated with transmeridian travel. The ability to travel rapidly across time zones has the unfortunate consequence of desynchronizing the circadian system[81]. The involvement of glucocorticoids in resetting the phase of the circadian clock has highlighted their possible contribution to the mechanisms underlying the effects of jet lag[82].

Glucocorticoids
Hormones produced by the adrenal cortex that are involved in carbohydrate and protein metabolism and also affect brain function. Cortisol (human) and corticosterone (rodent) are prime examples.

Jet lag
A syndrome that occurs upon crossing different time zones through transmeridian travel.

Box 2 | **Validity of animal models of depression**

Human depression is a complex disorder with a heterogeneous collection of symptoms that vary from patient to patient. This has made it difficult to identify the underlying mechanisms that are responsible for depression, a necessary step for the development of more effective treatments. Currently, it is not possible to completely model human depression in animals, and in particular it is difficult to model symptoms such as suicidality, excessive guilt and sadness[148]. However, there are animal models of some aspects of depression. It is important for these animal models to reflect the human condition in order to be valid. Indicators of such validity include similar symptom profiles (face validity), improvement in response to drugs that are effective in the human disorder (predictive validity) and involvement of similar neurological processes (construct validity)[149]. For example, exposure to chronic stress can induce depression in humans and depression-related behaviours in animal models. Chronic unpredictable stress, chronic social defeat stress and learned helplessness are some of the most widely used paradigms to induce depression-related behaviours in animals. These paradigms lead to changes in the animals that are reminiscent of human depression, such as the inability to derive pleasure (termed anhedonia), which is considered to be one of two cardinal symptoms that are obligatory for the diagnosis of depression in humans. Anhedonia can be assessed by measuring sucrose preference when animals are given a choice between a bottle containing plain water and another containing water and sucrose. Animals normally prefer the sucrose-containing water; however, animals showing increased depression-related behaviour exhibit a reduction in this preference task. Furthermore, these changes can be rescued with the administration of antidepressants.

For decades, animal models have been vital in furthering our understanding of the mechanisms underlying antidepressant efficacy and identifying potentially new, more effective antidepressants. A prime example has been in the mechanistic understanding of a rapidly acting antidepressant, ketamine. Although ketamine has the potential for abuse in humans owing to its psychomimetic side effects and hence cannot be prescribed, ketamine use in animal models has furthered our understanding of the molecular mechanisms that could underlie its rapid antidepressant effects[150,151]. This could lead to the production of new antidepressants that benefit from the mechanistic insights obtained from the ketamine studies.

The ability to model disorders such as depression in rodents enables the use of genetic, tracing and molecular tools that are widely available. These models and the available tools are essential to delineate and to refine the underlying mechanisms that cause the physiological changes that influence mood regulation. In fact, by using these tools in combination with optogenetics, we are now able to dissect the neural circuits that are involved in mood regulation. For example, optogenetic manipulation revealed the importance of the firing pattern of ventral tegmental area dopaminergic neurons in the regulation of depression-related behaviours[152,153].

Indeed, altered cortisol rhythms have been observed subsequent to transmeridian travel[83]. In addition, it was found that chronic transmeridian travel occurring at least once per week for 1 to 4 years resulted in cognitive deficits, which were possibly due to chronic circadian disruption and/or chronically increased cortisol levels[84]. A recent study showing that fluoxetine (Prozac) modulates levels of corticosterone to alleviate depression in mice maintained under irregular light schedules further suggests that this mechanism could underlie the depression associated with jet lag[85].

Shift work. The advent of artificial lighting has enabled us to utilize more hours of the day and create disruptive schedules such as shift work. Under these conditions, individuals are exposed to excessive night time light and alter their sleep–wake schedule, which causes asynchrony between the circadian and sleep systems. The attempt to remain awake at night and sleep during the day can lead to sleep deprivation, as daytime sleep tends to be more fragmented[86]. The risks associated with these disruptions include safety hazards and extensive health problems, which range from mood disorders to cancer[87]. Particular attention has been given to understanding the role of sleep deprivation in the genesis of these health problems. Sleep deprivation has been shown to result in cognitive function deficits, including negative effects on learning and memory, alertness and concentration[87,88]. The sleep disruptions that precipitate an episode of depression have been well characterized[48,50]. Interestingly, acute sleep deprivation has a robust antidepressant effect; however, the chronic sleep deprivation that is associated with shift work leads to mood disturbances[89–91].

Together, these three situations in which the light environment is altered provide evidence that light could have an essential role in modulating mood, probably through changes in the circadian and sleep systems. However, it is possible that light could modulate each function independently and hence, that irregular light patterns could directly influence mood. Indeed, irregular light schedules that do not cause circadian arrhythmicity and sleep deprivation were recently shown to induce mood changes[85].

Evidence from rodent research on mood disorders. Many laboratories have used rodents to study the mechanisms underlying the ability of light to influence mood through the circadian and sleep systems. Using rodents enables researchers to model mood disorders and examine the underlying physiological changes (BOX 2). In these studies, the light environment is altered and the effects on mood-related behaviours and cognitive functions are assessed (TABLE 1).

A short or long photoperiod can replicate seasonal light conditions and can be used to assess the behavioural effects of these seasonal light changes. Researchers using various diurnal and nocturnal rodent species have found that short photoperiods, such as those experienced during the winter months, induce increased depression-related behaviour and hippocampal learning deficits[92–96]. Corresponding alterations in hippocampal cell structure and long-term potentiation indicate functional deficits in this region in response to the shortened day length[96].

To model jet lag, researchers expose mice to shifts in the light–dark cycle that are similar to those that occur when flying across time zones[97] (Supplementary information S1 (figure)). Shifting the light–dark cycle results in the resynchronization of the circadian system to the new time. This temporarily disrupts the rhythmic expression of circadian-related genes within the SCN[98] and decouples the SCN from peripheral oscillators[99,100]. As in human studies, rodents show learning deficits in response to these light–dark cycle shifts. Studies have found that repeated shifts of the light–dark cycle result in impaired learning and memory in a series of behavioural tasks[101–104]. Furthermore, a recent study showed that one shift of the light–dark cycle was sufficient to attenuate recall in a contextual fear-conditioning task[105]. Together, these studies suggest that synchronization of the circadian system is important for cognitive function.

Long-term potentiation
A lasting increase in synaptic transmission in response to a strong correlated input.

Peripheral oscillators
Tissues, apart from the suprachiasmatic nucleus, that are capable of circadian rhythm generation.

Table 1 | **Rodent research in mood disorders using different light schedules**

Model	Animals used	Diurnal or nocturnal	Effect on circadian rhythms, locomotor activity and/or sleep architecture	Behavioural responses observed	Cortisol levels	Refs
Constant light	Mice	Nocturnal	Most mice become arrhythmic, although some animals remain rhythmic, either showing a lengthened period or split locomotor activity rhythms	• Induces depression-like behaviours (in the SPT and FST) • Decreases anxiety-like responses (in the OFT and EPM) • Impairs spatial memory (in the MWM)	↓	108, 159–161
	Wistar rats	Nocturnal	• Decreased amount of total time spent in NREMS (resting phase) and an increase in the number of REMS episodes (active phase) • Disruption of the pattern of circadian locomotor activity (an effect that is dependent on the light intensity) and body temperature	• Induces anxiety-like responses (in the OFT and EPM) • Impairs spatial memory (in the MWM)	↑	162, 167,168
Constant dark	Sprague-Dawley and Wistar rats	Nocturnal	The circadian rhythm period remains close to 24 hours, but the amplitude of the sleep–wake cycle decreases (increases sleep in the active period)	Induces depression-like behaviours (in the FST)	NT	163,167
Dim night time light exposure	Nile grass rats	Diurnal	No disruption of the pattern of circadian locomotor activity	Induces depression-like behaviours and learning alterations (in the SPT, FST and Barnes maze)	↑	124
	Siberian hamsters	Nocturnal	Reduced dark-phase activity	• Induces depression-like behaviours (in the SPT and FST) • Decreases anxiety-like responses (in the EPM)	↓	123,126, 164,165
	Mice	Nocturnal	No disruption of the pattern of circadian locomotor activity	NT	=	159
Short daylight	Sand rats	Diurnal	NT	• Induces depression-like behaviours (in the SPT and FST) • Induces anxiety-like behaviours (in the EPM but not in the OFT)	NT	92,93
	Nile grass rats	Diurnal	NT	• Induces depression-like behaviours (in the SPT and FST) • No anxiety-like behaviours (measured using a dark–light box) were observed	NT	166
Jet lag	Golden hamsters	Nocturnal	Minor changes in the pattern of circadian locomotor activity (desynchrony between internal and external time)	Impairs spatial memory (in a conditioned place preference paradigm)	↑	103
Phase shift protocol	Siberian hamsters	Nocturnal	Permanently eliminates circadian rhythms but preserves sleep architecture	Induces deficits in spatial working memory and in long-term object recognition memory (in the spontaneous alternation test and NOR)	NT	106
	Long Evans rats or albino rats	Nocturnal	NT	• Impairs spatial memory (in the MWM) • Produces retrograde amnesia (in the passive avoidance test)	NT	101,102
T7 cycle	Mice	Nocturnal	• Normal amount of total sleep and REMS • No disruption of the pattern of circadian locomotor activity (desynchrony between internal and external time)	• Induces depression-like behaviours (in the SPT and FST) • No anxiety disorders (measured using a dark–light box, the OFT and the EPM) were observed • Impairs spatial memory (in NOR and the MWM)	↑	5,85

↑ indicates increased levels; ↓ indicates decreased levels or blunted effect; = indicates that no differences were found. EPM, elevated plus-maze; FST, forced swim test; MWM, Morris water maze; NOR, novel object recognition; NREMS, non-rapid eye movement sleep; NT, not tested; OFT, open field test; REMS, rapid eye movement sleep; SPT, sucrose preference test.

Some light paradigms are capable of disrupting the circadian system to the point of causing circadian arrhythmicity (TABLE 1). For example, a light paradigm consisting of light pulses and phase delays was used to cause circadian arrhythmicity in hamsters. These hamsters showed hippocampal learning deficits, providing further evidence that the circadian system is required for normal learning and memory[106]. Similar results were observed in mice housed in conditions that simulated a 20-hour day, which consisted of a repeating 10 hours of light followed by 10 hours of dark. Mice were unable to synchronize their rhythms to this light–dark cycle and instead showed disrupted circadian rhythms[107]. This resulted in metabolic changes, and although these mice were able to learn a spatial memory task, they lacked flexibility when required to re-learn within the same task. These mice also showed decreased dendritic branching in the prefrontal cortex and mood-related behaviours associated with lesions to this region. To model the prolonged light exposure experienced as a result of artificial lighting, researchers have examined the effects of housing mice in constant light. This environment, depending on the light intensity, can cause circadian arrhythmicity, disrupt sleep–wake cycles and decreased locomotor activity. Mice housed in constant light showed increased depression-related behaviour and deficits in spatial learning and memory[108]. Interestingly, providing mice with an opaque tube in which to escape from constant light exposure rescued the increase in depression-related behaviour.

It is important to note that circadian arrhythmicity induced by surgical or genetic techniques causes antidepressant or manic effects[109,110] that are opposite to the effects of light-induced circadian arrhythmicity (TABLE 1). This suggests that the effects of constant light on mood are not solely an outcome of circadian rhythm disruption. Rather, it is possible that light has a direct, clock-independent role in influencing these functions. The effects of light may still require an SCN-dependent mechanism through which light information is either conveyed by or alters coupling of the SCN to downstream brain regions (FIG. 2). Alternatively, there may be a role for additional brain regions that are directly innervated by ipRGCs. Regardless of the brain circuit involved, light would disrupt normal regulation of brain regions that are important for mood, either by altering SCN firing patterns or by providing additional cues that would potentially disrupt normal activity.

These studies show that light-induced circadian rhythm disruption has a profound effect on multiple aspects of learning as well as mood-related behaviours in animal models. Additional investigation of the circadian, sleep and locomotor activity changes that occur in these environments will help to delineate the roles of each of these factors and produce a comprehensive model of how they interact together to influence affect and cognition (FIG. 1).

The direct pathway

Although the roles of light, sleep and circadian rhythms in mood regulation and cognitive function are seemingly interdependent, recent evidence for direct regulation of physiology by light may provide additional cellular mechanisms by which irregular light cycles lead to mood disorders.

Evidence for a direct pathway in humans. Initial studies on the effects of bright light on behaviour in humans found increased alertness and vigilance performance in response to light[111–113]. Functional imaging studies showed a correlation between increased alertness in response to light exposure and activation of the corresponding cortical and thalamic regions[114–116]. These neural responses were short-lived, declining minutes after light offset, which implies that light directly influences these regions. Using different light spectra, studies have found that regions of the brain that are involved in attention, alertness and emotional processes respond preferentially to 480 nm blue light, the wavelength that maximally activates melanopsin[117,118] (BOX 1). Furthermore, this light treatment also modulates cognitive function and emotional responses[117,118]. Evidence showing that the same effects of light are detected in blind subjects provided additional support for a role for ipRGCs in cognitive function[119] and is in line with other studies that indicate that ipRGCs have a role in signalling light for NIF functions in humans[120,121]. In patients with SAD, blue light increased responses to emotional stimuli in the posterior hypothalamus[122]. These patients also showed greater activation of regions of the brain that are involved in depression and reward, such as the locus coeruleus and dorsal raphe nucleus[122]. This suggests that light, in particular blue shifted light, is capable of modulating mood and cognitive functions, and that patients with mood disorders may have alterations in their responsiveness to this light information.

New discoveries in rodent models. Rodent models have also been used to understand the direct role of light on cognitive function and mood-related behaviours, although it should be noted that rodents cannot engage in human-like higher cognitive processes. A series of papers showed that exposure to dim light throughout the night resulted in increased depression-related behaviour[123–125]. However, the effects of dim light on hippocampal structure and function as well as the underlying mechanism differed depending on the rodent model used. The diurnal species, Nile grass rats, showed impaired spatial learning and reduced dendritic length in the dentate gyrus and CA1 regions of the hippocampus[124]. In hamsters, dim light at night reduced spine density in the CA1 region of the hippocampus[126]. Hamsters, however, also showed a decrease in locomotor activity in response to dim light at night. Therefore, it is possible that this lowered activity could contribute to the observed effects.

Although light influences mood, the circadian clock can also gate its effects, rendering light input beneficial or disruptive only at specific times of the day. Indeed, this has been shown in a study in which light exposure during the late portion of the night influenced despair-related behaviour in the forced swim test[127]. However, further research is needed to understand the apparent influence of the time of day on mood-related behaviours and the possible role of the circadian system.

Forced swim test
A test in which mice are placed in a water tank to measure depression-like states. Most depressed mice eventually develop an immobile posture, which is thought to indicate behavioural despair.

A recent study examined the effects of a light paradigm similar to shift work on mood-related behaviours and learning. Mice housed under an aberrant light paradigm were exposed to light during their active and inactive (sleep) phases but maintained intact circadian rhythms and normal sleep in terms of both amount and distribution of sleep stages (REM and non-REM sleep)[85]. These mice showed increased depression-related behaviours and a corresponding increase in baseline serum corticosterone. However, they showed no change in anxiety-related behaviours. Mice housed in this aberrant light cycle also showed hippocampal learning defects and a decreased ability to elicit long-term potentiation[85]. This study presents a new model that can be used to better understand the more direct role of light on mood and learning without disruption of the circadian system or sleep (FIG. 1).

Mechanisms underlying the direct effect of light. Although there is strong evidence implicating direct light input in the modulation of mood and cognitive functions, little is known about the retinal circuits that are responsible for signalling this light information to the brain. Studies in humans suggested that melanopsin may have a role in this process because it is preferentially activated by blue shifted light[118], but there was no direct evidence to support a role for melanopsin or ipRGCs in these functions. Additional studies found polymorphisms in the gene encoding melanopsin, *OPN4*, and decreased retinal sensitivity in the winter months in patients with SAD[128]. In rodents, light has been suggested to enhance the responses to subsequent stimulations in a cued fear-conditioning protocol. This response was only present if light was administered at recall (that is, after learning) and was dependent on the presence of rods and cones[129]. As rods and cones can signal light information through both ipRGCs and conventional RGCs, whether ipRGCs or conventional RGCs are responsible for conveying this information to the brain remains unknown.

To study the function of ipRGCs both as photoreceptors and as RGCs, ipRGCs were genetically ablated in mice through the expression of diphtheria toxin (aDTA) from the melanopsin locus[130]. In these *Opn4*$^{aDTA/aDTA}$ mice, conventional RGCs were not affected, and these animals were able to form images similarly to wild-type control mice. However, although *Opn4*$^{aDTA/aDTA}$ mice maintained intact circadian rhythms, they were completely incapable of circadian photoentrainment[130]. The intact rhythms, which have a period of slightly less than 24 hours, caused *Opn4*$^{aDTA/aDTA}$ mice to have regular bouts of activity that were not aligned to the light–dark environment. Thus, this study identified ipRGCs as the cells that are capable of signalling light information for circadian photoentrainment independently of vision and provided a great opportunity to study how irregular light schedules may affect mood and lead to sleep disturbances. Remarkably, mice lacking ipRGCs remained unaffected by an aberrant light cycle (an ultradian cycle consisting of 3.5 hours of light and 3.5 hours of dark; Supplementary information S1 (figure)). By contrast, wild-type mice showed increased depression-related behaviours and learning deficits[85]. This demonstrated a new role for the ipRGCs in conveying light information to the brain to mediate mood regulation and cognitive function. Importantly, it also showed that vision and conscious perception of light in the environment may have almost no role in mood-related behaviours that are associated with irregular light environments. Therefore, light could act as a central modulator of circadian rhythms, sleep and mood-related functions for an enhanced physiological outcome.

Perspectives

Circuits involved in aberrant light induced-depression. Remarkable advances in gene targeting methods and the discovery of sensitive reporter systems have set the stage for dissecting complex neuronal circuits. Several mice that express different reporters (such as the *Tau–lacZ* reporter or Cre recombinase) from the endogenous melanopsin locus have revealed diverse projection patterns from ipRGCs to several brain targets that are involved in depression and/or anxiety[19,27,131,132]. At present, five subtypes of ipRGCs have been identified based on their morphology and electrophysiological properties[30]. The principal target of M1 ipRGCs is the circadian pacemaker located in the SCN. However, ipRGCs (M1 and all non-M1 cells) also project to preoptic and lateral hypothalamic areas such as the VLPO and the ventral subparaventricular zone, which control sleep induction and general activity levels, respectively. In addition, ipRGCs innervate some limbic regions such as the lateral habenula and the medial amygdala, highlighting the possible direct role of light in the regulation of mood and cognitive functions (FIG. 2).

How could one uncover the brain region (or regions) that underlie the direct effects of light on mood? A recent discovery showed that ipRGCs can be molecularly differentiated based on the expression of the BRN3B (also known as POU4F2) transcription factor[133]. BRN3B is expressed in all non-M1 cells and in the majority of M1 cells. In animals in which all BRN3B-positive ipRGCs (all non-M1 and most M1 cells) were ablated, it was shown that the remaining M1 BRN3B-negative cells, which represent ~10% of total ipRGCs, provide the major input to the SCN[133], with BRN3B-positive ipRGCs providing only a minor input. In addition, the BRN3B-negative ipRGCs do not project to areas outside the SCN that regulate mood. Therefore, these animals, if placed under aberrant light conditions, could be used to determine the role of the SCN, versus other brain targets that receive ipRGC input, in mood regulation (FIG. 2). A complementary animal model in which only the SCN-projecting ipRGCs are ablated will be essential for understanding the roles of other brain regions in mood regulation.

Defining a single population of retinal neurons that, if activated at the wrong time of the day, causes depression-like symptoms and learning deficits affords us the possibility of identifying new areas that may be important for these functions. An approach that might be taken to achieve this goal would involve the expression of synaptically tagged channelrhodopsins in the ipRGC population and stimulation of ipRGC terminal fields in the brain at different times of the day and night to examine whether depression symptoms and learning deficits are observed.

Polymorphisms
Natural variations in a gene or a particular DNA region. These genotypic differences give rise to more than one morph, evidenced as differences in the phenotype.

Genetic mouse models can provide evidence that a specific brain region is required for light modulation of mood-related behaviours. Research using imaging technology in humans will confirm whether similar brain regions are activated in response to light. Recent observations show dynamic changes in activity in regions involved in mood and cognitive functions in response to light in humans[114–118,134]. The role of melanopsin in mediating these light-dependent changes is supported by imaging studies carried out in blind subjects and by using the wavelength of light that maximally activates this photopigment[116–119]. Research in this area is also beginning to provide new insight into the changes in light-dependent neural responses in mood disorders such as SAD[122]. The findings that light-dependent modulation of brain activity can depend on the circadian system and sleep[135,136] make it essential to dissect the influence of light on these brain regions under conditions in which the circadian clock and sleep are perturbed, such as in people with shift-work schedules or people experiencing jet lag.

Future investigations should be directed towards understanding the cellular and molecular mechanisms through which aberrant light causes these symptoms. Does aberrant light change the expression of genes, synaptic connectivity or neurotransmitter composition in specific brain regions? Does it affect neurogenesis in the brain? How do these changes lead to depression symptoms and learning deficits? If combined, these studies will expand the understanding of how light modulates mood and learning for improved physiology.

Effects of light on central and peripheral clocks. Different environmental stimuli may play a part in inducing depression-like behaviours. Light (particularly artificial illumination at night) is one of the strongest of these stressors (BOX 3). The circadian timing system uses light to adjust the SCN and synchronize it with the external environment. The integration of external signalling with the autonomous clock properties of the central pacemaker results in the transmission of timing information to peripheral clocks and brain areas involved in complex behaviours. Could irregular light schedules lead to asynchrony between the phases of brain and peripheral oscillators that then lead to depression? For such a dissociation to occur, brain regions that influence affect, that have an endogenous clock, that are controlled by the central pacemaker and that receive light input directly from ipRGCs would have to exist. Two such areas satisfy these requirements: the amygdala and the lateral habenula. The amygdala projects to the ventral tegmental area and the hippocampus — two brain regions that are known to have a role in depression. The lateral habenula also projects to the ventral tegmental area and the raphe nucleus, and forms a node of connection between limbic nuclei, hypothalamic brain regions and brainstem monoamine neurons[137]. A comprehensive evaluation of the phase relationship between the peripheral clocks that influence mood and the central pacemaker should be undertaken to understand the mechanisms by which irregular light causes depression.

Environmental lighting conditions. Extreme lighting conditions or schedules can affect mood and behaviour. Common examples of this are shift-work schedules or transmeridian travel, as described above. A fundamental question is how ipRGCs signal light information to regulate mood and cognitive functions. The use of genetically modified mouse lines will open the possibility to study the relative contributions of classical photoreceptors (rods and cones) versus the intrinsic melanopsin-related response of ipRGCs under aberrant light conditions.

Understanding the changes in light exposure, cell circuits and pathways that lead to mood and cognitive changes will be helpful for creating new strategies to treat mood disorders. Research in this area has so far sought to use behavioural interventions to alter the circadian system and restore normal mood. Perhaps the most

Box 3 | **Irregular light as a risk factor for disease**

Light has a profound impact on physiology. It exerts a potent influence on the circadian system, which coordinates and appropriately times physiological functions, including hormone secretion, metabolism and sleep[3]. Light has also been found to directly influence sleep, alertness and cognitive function[5,6,115,117]. Given the strong effects light can have on physiology and behaviour, regular light exposure is important for the proper maintenance of physiological processes.

The advent of artificial lighting has enabled us to utilize more hours of the day. This has initiated the restructuring of the workday and the shift away from activity in alignment with the solar day. Although this has been thought to increase productivity, it comes at a considerable cost, which is irregular night time light exposure. The impact that light has on physiological functions makes irregular light exposure potentially detrimental to health and wellness. Indeed, irregular light environments can be implicated in the manifestation of health problems observed, for example, in shift work and jet lag. These range from cardiovascular disease to mood disorders. Irregular light exposure thus becomes an important risk factor for developing health problems.

This risk has the potential to be exacerbated in the presence of additional factors, such as chronic stress or genetic susceptibility factors for mood-related disorders. Several genetic factors have been implicated as the underlying cause of psychiatric diseases, and chronic stress is known to influence circadian rhythms and sleep, and has deleterious effects on health[154–158]. Compounded with the presence of irregular light exposure, these factors could interact and lead to a higher incidence of depression and other neurological disorders that are prevalent in society.

Despite the importance of light, it is surprising how little is understood regarding the mechanisms through which light affects physiological functions. A better understanding of the underlying mechanisms of how light affects mood-related behaviours will have a major impact on increasing our understanding of mood and cognitive deficits, and it would provide impetus to change the way we expose ourselves to light during day–night cycles for the enhancement of health.

well known of these treatments is bright light therapy. The use of light treatment, particularly for SAD, has been shown to be effective in ameliorating depression symptoms. In fact, blue light therapy has been found to be particularly effective in the treatment of SAD[138,139]. Bright light therapy has also been found to be useful for non-seasonal depression and bipolar disorder. These disorders are widely treated with medication; however, a considerable lag time (usually ~2 weeks) exists between the start of antidepressant treatment and response to treatment. Bright light therapy was found to decrease this latency when combined with antidepressant treatment[140]. It is thought that the morning is the most effective time for bright light treatment. However, this is not true in all cases, and the best approach is to individualize treatments by taking into account a particular patient's circadian rhythms. Determining the pathways by which ipRGCs affect mood would shed light on how better lighting conditions (in terms of wavelength, intensity and exposure) can create an effective treatment. Understanding the role of melanopsin-based phototransduction in light induced-depression will be important in order to design lighting conditions enriched in red wavelength at night that still allow individuals to see without activating melanopsin and hence cause minimal disruption to circadian, sleep and mood systems.

Final conclusion and future insights. At present, treatments for mood disorders are still limited and the development of more effective treatments for these disorders is required. A better understanding of the connections of ipRGCs in the brain and their influence on complex behaviours such as depression and cognitive functions will be the first step towards understanding the role of light in these complex behaviours. The use of aberrant light schedules as a new model for the induction of depression is a new avenue to study the direct effect of light on depression, independently of circadian arrhythmicity or sleep disruption. Future studies using aberrant light cycles should be designed in order to provide a better understanding of the relationships between different brain areas involved in mood and learning. Understanding the interaction between light and complex behaviours will lead to more effective architectural designs for lighting environments in schools and work, leading to enhanced mood and better learning abilities.

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Competing interests statement
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