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REVIEW

Influence of the modern light environment on mood

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Humans and other organisms have adapted to a consistent and predictable 24-h solar cycle, but over the past ~130 years the widespread adoption of electric light has transformed our environment. Instead of aligning behavioral and physiological processes to the natural solar cycle, individuals respond to artificial light cycles created by social and work schedules. Urban light pollution, night shift work, transmeridian travel, televisions and computers have dramatically altered the timing of light used to entrain biological rhythms. In humans and other mammals, light is detected by the retina and intrinsically photosensitive retinal ganglion cells project this information both to the circadian system and limbic brain regions. Therefore, it is possible that exposure to light at night, which has become pervasive, may disrupt both circadian timing and mood. Notably, the rate of major depression has increased in recent decades, in parallel with increasing exposure to light at night. Strong evidence already links circadian disruption to major depression and other mood disorders. Emerging evidence from the past few years suggests that exposure to light at night also negatively influences mood. In this review, we discuss evidence from recent human and rodent studies supporting the novel hypothesis that nighttime exposure to light disrupts circadian organization and contributes to depressed mood.

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INTRODUCTION

Life on Earth has adapted to a consistent and predictable 24-h solar cycle. To anticipate patterns in the environment, individuals synchronize internal biological rhythms to the external world, primarily using light information. During the past ~130 years, however, the invention and widespread adoption of electric light has led to 'round-the-clock' societies. Instead of aligning with the environment, individuals respond to artificial light cycles created by social and work schedules. Exposure to artificial light at night (LAN) has become pervasive (Figure 1). Virtually every individual living in the United States and Europe experiences this unnatural light exposure, and moreover about 20% of the population performs shift work.[1,2] Exposure to LAN may obscure entrainment of biological processes to external conditions, potentially leading to misalignment among physiology, behavior and the environment.

Furthermore, chronic disruption of circadian timing may have implications beyond dysregulated biological rhythms. In mammals, circadian photoentrainment is mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) that project light information to the suprachiasmatic nucleus (SCN) in the hypothalamus, regulating circadian rhythms. However, ipRGCs also project to regions involved in mood regulation, such as the prefrontal cortex, hippocampus and amygdala,[3] suggesting that unnatural light exposure has the potential to influence mood as well. As modern life has allowed humans to manipulate lighting easily and has led to unnatural exposure to LAN, the prevalence of major depressive disorder (MDD) has increased in parallel.[4] Accumulating evidence from the past few years suggests that nighttime light exposure may have serious consequences for circadian timing and mood. In this review, we discuss evidence from recent human and rodent studies supporting the novel hypothesis that nighttime exposure to light disrupts circadian organization and contributes to depressed mood.

PHOTOENTRAINMENT

Circadian rhythms are generated by the SCN, a molecular clock located in the hypothalamus, and entrained to the external environment primarily using light information sent directly from the retina to the clock. A transcription–translation feedback loop in the SCN produces endogenous rhythms of approximately 24 h, but the gene and protein components of this cycle can be modulated by light to maintain synchronization with the environment. In the absence of light and dark input, the endogenous clock becomes out of phase with the external environment, so correctly timed light information is essential to biological timekeeping. In mammals, the retina is the sole mechanism of light detection, consisting of image-forming photoreceptors, called rods and cones, and non-image-forming photoreceptors called ipRGCs. In contrast to rods and cones, ipRGCs are depolarized in response to light and are largely responsible for circadian photoentrainment.[5]

Light detected by ipRGCs activates a unique photopigment called melanopsin, which is maximally sensitive to blue wavelengths (~480 nm) and minimally sensitive to longer, red wavelengths (>600 nm).[6] This means that blue wavelengths exert a more potent influence on the circadian system. Notably, in the United States nighttime use of incandescent bulbs, which produce light of longer yellow range wavelengths, is being replaced by compact fluorescent light bulbs, which contain the blue wavelengths that maximally activate ipRGCs.[7] Activated ipRGCs project to the SCN directly through the retinohypothalamic tract and indirectly through the intergeniculate leaflet. Information sent via the retinohypothalamic tract reaches the SCN through a single glutamatergic synapse. This process is similar in both nocturnal and diurnal species; LAN triggers Fos induction in the SCN of both.[8,9]

The SCN projects axons to the paraventricular nucleus of the hypothalamus (PVN) and to the thalamus (Figure 2). Thalamic

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Figure 1. Worldwide artificial light at night. Inset shows detailed view of North America. Images are composites acquired by the NASA Suomi NPP satellite in 2012.

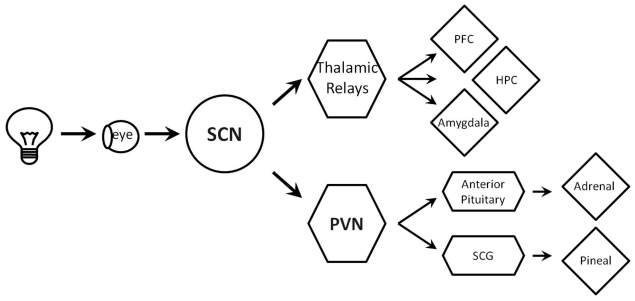

Figure 2. Potential pathways through which light at night (LAN) may influence mood. HPC, hippocampus; PFC, prefrontal cortex; PVN, paraventricular nucleus of the hypothalamus; SCG, superior cervical ganglion; SCN, suprachiasmatic nuclei.

relays of the SCN project to regions directly involved in mood regulation, such as the prefrontal cortex, hippocampus and amygdala. Projections through the PVN to the pineal gland regulate melatonin secretion, which is responsible for entraining peripheral clocks in cells and tissues throughout the body. And projections through the PVN to the adrenal gland regulate glucocorticoid output. From these examples, it seems reasonable to suggest that temporally aberrant cues in the environment arising from artificial LAN could cause desynchronized biological rhythms at multiple levels.

Melatonin

Pineal melatonin warrants brief discussion on its own because its production is under direct control by light. Typically melatonin is rhythmically secreted by the pineal gland during the night, where it is released directly into systemic circulation, having many different physiological roles throughout the body.[10] Its secretion is potently inhibited by light in an intensity-dependent manner.[6] Evidence suggests that only 1 h of exposure to ~45 photopic lux can decrease plasma melatonin concentrations by ~60% in healthy human volunteers.[11] In hamsters, light levels as low as 1.08 lx are sufficient to significantly suppress pineal melatonin content.[12] During the night, suppressed melatonin levels can disrupt physiological timekeeping. For example, melatonin regulates clock gene oscillations in the pituitary and pars tuberalis in mice and hamsters.[13,14]

CIRCADIAN DISRUPTION AND MOOD

A role for the circadian system in mood is already well-established. A host of rhythm-related disturbances have been noted in association with major depression and other mood disorders; and on the other hand, environmental perturbations of the circadian system provoke mood disturbances in some individuals.[15–17] Any unnatural timing of light exposure, or lack of appropriate light/dark cues in the environment, can cause misalignment between internal biological processes and the external environment, putatively leading to impaired mood. To illustrate this point, there are several instances in which obscured environmental lighting cues lead to depressed mood.

Seasonal affective disorder (SAD) is one prominent example. At temperate latitudes, seasonal affective disorder affects nearly 10% of the population.[18] It is characterized by recurrent winter depression, with symptoms manifesting during the short day lengths of winter when daylight exposure is low, and symptoms remitting during the spring and summer. Lack of sufficient daytime light is thought to cause a phase shift in the rhythm of pineal melatonin secretion. Without bright morning light to inhibit melatonin production, secretion persists into the daytime, leading to desynchronization between internal timekeeping processes and the external environment. Although melatonin concentrations are not suppressed, as they may be with LAN exposure, there is misalignment between the rhythm of secretion and the environmental light cycle. The presence of an appropriate and correctly timed melatonin signal may be more important to circadian regulation and mood than absolute melatonin concentrations. Morning bright light therapy, particularly blue wavelengths, may be used to synchronize the circadian system to the appropriate time of day.[19]

Evidence from animal models supports a role for day length in mood.[20] Nocturnal Siberian hamsters exposed to short, winter-like, day lengths develop depressive-like responses in the forced swim test and anxiety-like responses in the elevated plus maze.[21] Two

diurnal rodent species, fat sand rats (*Psammomys obesus*) and Nile grass rats (*Arvicanthis niloticus*), also exhibit depression-like behavior in the forced swim test after exposure to very short photoperiods (5 h light/19 h dark).[22,23] Bright light therapy, one current treatment for seasonal affective disorder in human patients, reverses some of the depressive responses in fat sand rats.[24]

A complete lack of light/dark cues in the environment may also elicit cognitive and behavioral impairments. Rodents exposed to constant light become arrhythmic in terms of locomotor activity and other biological rhythms, a major circadian disruption. After 3 weeks of constant light exposure, rats exhibit impaired spatial learning and memory,[25] and mice show impaired performance in the Morris water maze and reduced hippocampal neurogenesis.[26]

In contrast, light deprivation in the form of constant darkness may provoke depression-like changes in rodents too. Mice and rats exposed to constant darkness for several weeks develop immobility in the forced swim test, as well as other depression-like behaviors.[27] There is some evidence that constant darkness causes neuronal damage to monoamine systems,[28] including increases in apoptosis in several brain regions. Other evidence suggests that constant darkness increases proinflammatory cytokine levels in the brain and periphery, and that the depression-like responses are interleukin-6-dependent and mediated through the nuclear factor-κB signaling pathway.[27]

These examples serve to highlight the importance of light in regulating behavior and mood. Proper alignment among biological rhythms, behavior and the environment requires a balance in the amount of light and dark to which an organism is exposed. Tipping that balance in either direction can have profound consequences for physiology and mood.

POPULATIONS EXPOSED TO LAN

Over 99% of individuals living in the United States and Europe experience nightly light pollution.[29] Streetlights illuminate the bedroom, television and computer screens glow in the home at all hours, and work and social demands keep the lights on. LAN can be invasive for these individuals, but for certain populations, exposure to LAN is even more pronounced.

For example, in industrial economies, ~20% of the population are shift workers.[2] These are often factory workers, medical staff, flight attendants and others working in environments that require bright lights during night shifts. Such bright and chronic LAN exposure provokes several physiological changes. Exposure to LAN of $\leqslant$200 lx, levels easily encountered during night shift work, can suppress melatonin secretion and other circadian responses in humans.[30] Shift work is associated with health consequences, including increased negative affect and feelings of helplessness.[31] Also, the World Health Organization (WHO) recently cited shift work as a probable carcinogen.[32] Following this announcement, Denmark became the first nation to compensate women who developed breast cancer after working night shifts.[33]

By the same token that night shift nurses are affected by LAN, their patients may be similarly affected. Light readings obtained at a Midwest hospital SICU demonstrate that lights were illuminated at least 30 min out of every hour throughout the night, often when no nursing or care activity was being performed.[34] LAN in this context may negatively affect patient outcome by disrupting sleep and biological rhythms.[35]

Although artificial LAN is most common, natural LAN may be experienced by individuals living at certain latitudes. During the summer at northern latitudes near the Arctic Circle, a phenomenon referred to as 'midnight sun' occurs, in which the sun remains visible throughout the night. Scandinavian countries, for example, experience sunlight almost 24 h each day during certain times of the year. In parts of Finland's territory lying north of the Arctic Circle, the sun does not set for 60 days during the summer. The circadian system is not adapted to such extremes in the light environment. At least one study has reported that the number of violent suicides in these regions increases dramatically during times of 'midnight sun', suggesting that even naturally occurring LAN can negatively influence mood and behavior.[36]

In contrast, one population in the United States excluded from many types of LAN exposure is the Old Order Amish. The Amish do not use televisions or computers, which are a major source of LAN exposure among the general population, and LAN exposure is minimal. Interestingly, the Amish display greatly reduced cancer rates compared with the general population.[37] Incidence of depression and other psychiatric disorders is also reduced.[38] Of course, other lifestyle factors may contribute to better health in this population, but the Amish represent an interesting opportunity to understand the effects of modern lifestyle choices on mood.

PHYSIOLOGICAL EFFECTS OF LAN

Clearly, exposure to LAN is quite pervasive in Western societies and several mechanisms exist by which this unnaturally timed exposure may influence mood. For one, at least in diurnal species, LAN is likely a sleep disruptor. There is a large literature implicating sleep disruption or deprivation in negative mood regulation (reviewed in Tsuno *et al.*).[39] As many as 50–90% of depressed patients complain of poor sleep quality and ~20% of insomniacs are clinically depressed.[39] A relationship exists between disrupted sleep and depression and chronic exposure to LAN may be one contributor. Recent rodent studies suggest, however, that LAN can influence mood independent of sleep disruption, and this evidence will be reviewed in detail later.

Pineal melatonin secretion is also disrupted by LAN and accumulating evidence suggests that melatonin is related to mood. Agomelatine, a melatonin-receptor agonist and serotonin ($5\text{-}HT_{2C}$) receptor antagonist, belongs to a new class of melatonergic antidepressants.[40,41] In rodents, melatonin administration prevents stress-induced depressive-like behaviors and reductions in hippocampal dendritic complexity.[42] Melatonin has positive effects on hippocampal cell proliferation[43] and can stimulate neurotrophin production in the brain—both of which are responses associated with antidepressants.[44]

Direct dysregulation of circadian clock genes could also underlie depression associated with LAN exposure. Some clock genes are directly regulated by light. For example, *Per1* expression in the SCN is directly stimulated by acute LAN exposure.[45] Disruption of clock gene oscillations, particularly within limbic regions that receive projections from the SCN, may contribute to altered mood. Over time, upsetting the daily oscillation of clock genes and their protein products may alter the function of important mood-regulating systems—for example, it may alter expression and activity of neurotransmitter receptors implicated in mood, and clock gene variants have been associated with risk of mood disorders in humans (reviewed by McClung[16]). The precise role of clock genes in mood regulation remains undetermined, as does the question of whether acute disruption of clock genes is sufficient to provoke altered mood regulation or whether disruption over the long term is required.

Similarly, diurnal variations in hormone secretion may be disrupted by LAN, particularly within the hypothalamic-pituitary-adrenal (HPA) axis. Recall that the PVN receives direct input from the SCN, which projects to the pituitary and then the adrenal. Cortisol, a major stress hormone released by the adrenal gland, has been implicated in depression and atrophy of the hippocampus when levels are chronically elevated.[46] In depressed patients, the diurnal rhythm of cortisol concentrations tends to be lost, and levels are consistently high throughout the day.[47]

It is possible that LAN may act at any or all of these levels to provoke altered mood regulation. Indeed, it is likely that many

layers are implicated at once, causing a complex interplay of misaligned systems. Disruption at one level could also provoke further dysregulation at another; for example, suppressed melatonin secretion could in turn further disrupt diurnal clock gene oscillations throughout the body, compounding the effects of LAN exposure.

EVIDENCE LINKING LAN TO MOOD

Humans

Several studies in shift-working populations have linked night work to negative affect. Among US workers, regular shift work has detrimental effects for sleep and social factors, and is associated with high prevalence of MDD, with a higher rate among women than men.[48] The prevalence of MDD during or after night shift work is greater than the general population prevalence, but reflects the same trend of disproportionately affecting women (22.6% of female shift workers vs 13.4% of male shift workers).[48] Long-term shift work is not necessary to see these effects, however. Among young student nurses performing night shift work for the first time, feelings of helplessness, loss of control, apathy and low social support were perceived after only 3 months of night work.[31] With longer term exposure (up to 20 years of shift work), there is an increased lifetime risk of MDD.[48] One of the proposed treatments for problems associated with night shift work is bright light exposure during the night to phase shift the biological clock to align with the work schedule, thus improving alertness at work and facilitating sleep during the day.[49] A limitation of this approach is the difficulty maintaining such a schedule. On weekends and 'off' days, workers quickly revert back to synchronize with environmental and social cues.

Although increased depressive symptoms have been well-documented among shift workers,[31] these studies are limited in establishing an exclusive link to LAN due to the other variables involved, such as sleep disruption and episodic (for example, weekend) phase shifts. Jet lag is another modern change that is thought to be related to changes in affect.[50] Patients admitted for psychiatric emergencies are more likely to exhibit depression or mania after travel across time zones compared with those admitted with no recent travel history, and those traveling westbound show the most symptoms of depression.[51] Even from a biological perspective, in flight attendants transmeridian travel with short recovery time between trips is associated with reduced temporal lobe volume that is related to cognitive deficits.[52]

Unfortunately, these studies are limited by the number of variables, as both shift work and jet lag tend to disrupt sleep and social schedules in addition to lighting exposure. It is difficult to obtain direct data linking LAN to mood in human subjects because such studies would entail careful control of several environmental variables over many weeks.

Animal models

Animal models allow mechanistic studies into the role of LAN in mood regulation, without the confounding variables associated with human studies, and allow investigation into the molecular basis of LAN effects. A summary of results from these studies is presented in Table 1. Our laboratory recently developed a model of dim (5 lx) LAN exposure using Siberian hamsters. This light intensity is similar to levels that may be easily encountered by the average individual through the use of televisions, computers and e-readers at night. One general limitation of rodent models, however, is that species differ in their responsiveness to a particular intensity. For example, melatonin is suppressed by about 1.08 lx in Syrian hamsters, whereas 45 lx decreases melatonin levels in humans.[11,12] It is not clear how other circadian responses to a given intensity may compare between different species. An alternate model is to study the effects of housing rodents in constant light (LL) without varying light intensity; however, rodents become arrhythmic under these conditions, making it difficult to obtain interpretable results.[53] Hamsters exposed to 5 lx dim LAN, however, remain entrained to the light–dim light cycle, at least in terms of locomotor activity. Some changes in activity occur, however, as homecage locomotor activity is slightly reduced during the dim light phase compared with typical dark phase activity levels and fast Fourier transformation analysis reveals slight decrements in the strength of the 24-h rhythm. Eliminating the LAN rapidly reverses this effect.[54] Entrainment of other diurnal rhythms may be influenced, however. The daily expression patterns of PER1 and PER2 proteins in the SCN are altered with LAN exposure; in both cases, the rhythm is weakened, but BMAL1 expression remains intact.[55] The daily fluctuation in plasma cortisol concentrations is abolished as well.[55]

There are two advantages to using Siberian hamsters for LAN studies. First, they express melatonin receptors in the brain and, unlike most inbred strains of laboratory mice, they produce detectable levels of pineal melatonin. The extent to which melatonin is implicated in LAN effects on mood is still unclear, as depressive responses after exposure to LAN have been reported in at least one melatonin-deficient mouse strain.[56] However, because melatonin suppression may likely occur in humans exposed to LAN, using a melatonin-proficient animal model may increase the translational relevancy to humans. Second, unlike humans, hamsters are nocturnal, meaning that LAN exposure occurs during their active period, allowing us to separate the effects of LAN and disrupted sleep. LAN does indeed influence mood and physiology in at least one diurnal species, Nile grass rats; however, sleep quality was not investigated in these studies, making it difficult to attribute solely the findings to LAN.[57]

Our studies have consistently demonstrated that dim LAN provokes depressive-like responses in hamsters.[54,58] Because of the difference in activity levels during the dark or dim phase, behavioral testing for activity-dependent measures must be performed during the light phase, when activity levels are equivalent between groups. After 4 weeks of exposure to nightly 5 lx LAN, hamsters tested during the light phase display more immobility in the forced swim test, typically interpreted as behavioral despair, and reduced preference for sucrose solution, an anhedonic-like symptom.[54,58] Within 2 weeks of eliminating LAN, however, behaviors in both of these tests resemble those of hamsters exposed only to dark nights.[54] One method of validation for behavioral assays of depressive-like response is to measure behavior after treatment with an antidepressant drug that is known to be effective in humans. Although Siberian hamsters housed in dim LAN for 4 weeks develop depressive-like symptoms in the forced swim test, 2 weeks of treatment with the selective serotonin reuptake inhibitor, citalopram, ameliorates the symptoms, supporting the validity of this model.[59]

The complete mechanism underlying these behavioral responses remains unknown, but we have observed stark changes to the hippocampus, one brain structure implicated in the pathophysiology of MDD. Depressed patients often have hippocampal atrophy[60–62] and dysregulation of many hippocampal-related systems, such as stress coping and memory (reviewed in Nestler *et al.*).[63] Similarly, loss of hippocampal dendritic spines and reduced dendritic complexity are observed in animal models of chronic stress and depression.[64–66] In these models, expression of brain-derived neurotrophic factor is typically reduced in the hippocampus, but antidepressant drugs enhance its expression.[67] Hamsters exposed to 4 weeks of dim LAN have reduced dendritic spine density on hippocampal CA1 pyramidal neurons, although no other changes to overall dendritic complexity or to neurons within other hippocampal subregions are apparent, and reduced mRNA expression of brain-derived neurotrophic factor in

Table 1. Summary of evidence from rodent studies demonstrating effects of LAN on mood and cognition

	Species	*Active period*	*Light manipulation*	*Findings—behavior*	*Findings—brain*
Fonken *et al.*[56]	Mouse (Swiss Webster)	Nocturnal	LL	↑ FST immobility ↓ Sucrose preference	None measured
Bedrosian *et al.*[58]	Siberian hamster	Nocturnal	5 lx dim LAN	↑ FST immobility ↓ Sucrose preference	↓ HPC spine density
Fujioka *et al.*[26]	Mouse (C57bl/6)	Nocturnal	LL	↓ Spatial learning	↓ HPC neurogenesis
Fonken *et al.*[57]	Nile Grass Rat	Diurnal	5 lx dim LAN	↑ FST immobility ↓ Sucrose preference ↓ Spatial learning	↓ HPC dendritic length
LeGates *et al.*[70]	Mouse (B6/129 F1 hybrid)	Nocturnal	Ultradian T7 cycle	↑ FST immobility ↓ Sucrose preference ↓ Spatial learning	ipRGCs necessary Reversed by fluoxetine
Bedrosian *et al.*[54]	Siberian hamster	Nocturnal	5 lx dim LAN	↑ FST immobility	Reversed by citalopram
Bedrosian *et al.*[55]	Siberian hamster	Nocturnal	5 lx dim LAN	↑ FST immobility ↓ Sucrose preference	↓ HPC *Bdnf* mRNA ↑ HPC *Tnf* mRNA

Abbreviations: FST, forced swim test; HPC, hippocampus; ipRGCs, intrinsically photosensitive retinal ganglion cells; LAN, light at night.

the hippocampus.[54] Both of these effects are reversed after eliminating LAN.

In addition, the hippocampus is disproportionately vulnerable to inflammation compared with other brain structures because of its high expression of receptors for proinflammatory cytokines such as IL-1β and tumor necrosis factor-α.[68] Neuroinflammation may have a role in depressive-like behavior provoked by a variety of types of circadian disruption. As mentioned, exposure to constant darkness induces depression-like behavior and increased interleukin-6 levels, which are ameliorated by blocking nuclear factor-κB signaling. Furthermore, mice with a deletion of interleukin-6 are resistant to the behavioral effects of exposure to constant darkness.[27] In our experiments, hamsters exposed to dim LAN show increased tumor necrosis factor-α expression in the hippocampus; treatment with a pharmacological inhibitor of tumor necrosis factor-α prevents depressive responses in the forced swim test after exposure to LAN.[54] This link between depression-like behavior provoked by circadian disruption and neuroinflammation is not surprising. A role for proinflammatory cytokines in the pathogenesis of depression has been proposed and recent evidence demonstrates a direct molecular pathway whereby disruption of circadian clock proteins enhances expression of cytokines within the brain.[69]

Our results suggest that exposure to LAN alters mood by disrupting circadian rhythms, but to answer the question of whether unnatural light exposure on its own can directly impair mood, a model of aberrant light exposure was used that does not strongly influence circadian timing or sleep.[70] Mice were exposed to an ultradian cycle of 3.5 h light and 3.5 h dark (termed T7), which lengthens the period of body temperature and locomotor activity rhythms, but maintains diurnal fluctuations in PER2 expression in the SCN and total sleep. After 2 weeks of exposure to the ultradian light cycle, mice exhibited increased depressive-like responses in the forced swim and sucrose preference tests. Further, the mice had impaired learning and memory performance accompanied by reductions in hippocampal long-term potentiation. Much like the results we have obtained using dim LAN, treatment with an selective serotonin reuptake inhibitor reversed the depressive responses. These behaviors seem to occur through ipRGC projections because mice lacking the gene for melanopsin do not develop depressive responses after exposure to the ultradian light cycle.

The results of this study[70] led the authors to conclude that LAN influences mood regulation directly, without disrupting circadian rhythmicity. This is an intriguing hypothesis, particularly in light of evidence that ipRGCs project to mood-regulating regions of the brain, although whether these pathways are direct connections or projections through the SCN remains unclear.[71] However, several technical considerations may limit the conclusions drawn from this study. For one, time of day for behavioral testing procedures was not described, making it unclear whether differences in locomotor activity levels evident under the T7 cycle may have contributed to the results. In addition, PER2 expression was measured relative to the activity of the animal. In other words, time points were chosen based on zeitgeiber time for control mice in a 24-h light cycle, but based on circadian time for T7 mice. It is not clear whether behavioral testing was similarly coupled. Presumably, behavioral measurements were performed in both groups at one time of day, thus uncoupling depressive-like behaviors from the activity rhythm. Time of day effects on behavioral performance in these tasks is well-established and particularly the forced swim test is highly dependent on the activity level of the animal. It is possible that the effects ascribed to the T7 cycle may actually reflect testing occurring during different circadian phases for each group. Furthermore, the mechanism through which these changes may occur remains undetermined. Although it is tempting to speculate that unnatural timing of light exposure may contribute to impaired mood, more investigation will be necessary to parse out circadian effects from direct light effects.

Nevertheless, converging evidence seems to point towards negative effects of LAN on mood regulation. An important question arising from this collective work is how to prevent the deleterious effects of LAN when exposure cannot be avoided. One possibility may be to manipulate the wavelength of light exposure. As mentioned previously, the melanopsin-expressing ipRGCs responsible for projecting light information to the circadian system are minimally responsive to red wavelength light. Replacing standard bulbs with red ones where possible, or using glasses that only transmit red wavelengths, may be an effective preventative against the disruptive effects of LAN. We have observed reduced effects of dim red LAN on hamster depressive responses, compared to white or blue LAN, along with reduced Fos activation in the SCN following red LAN exposure.[72] Clearly, LAN has a variety of effects on the brain and circadian rhythms, each potentially contributing individually or in concert with others to regulate mood.

IMPLICATIONS AND FUTURE DIRECTIONS

The incidence of depressive disorders has increased significantly in recent decades,[4,73,74] in parallel with the expansion in the use of electric LAN. Particularly, urban-dwelling individuals and night shift workers are exposed to artificial LAN on a chronic basis. For these people, LAN may be considered as a modern circadian

disruptor. Given the evidence for disrupted circadian processes in depression, excessive LAN exposure could be one factor contributing to depressed mood among vulnerable individuals. Artificial and unnaturally timed light from the environment could disrupt physiological timekeeping, leading to misalignment of various biological rhythms, or could act directly to influence mood. Studies using animal models have been useful thus far to identify a link between LAN and mood, but such a link in humans remains to be demonstrated. A first step would be to perform thorough correlational analyses through epidemiological analysis. Within this past decade, epidemiological work paved the way toward identifying the relationship between LAN and breast cancer, which is now officially recognized by the WHO and American Medical Association. Such studies should not only focus on shift workers but also include individuals experiencing low levels of LAN at home. Example studies are already beginning to identify relationships between LAN and obesity.[75] From an historical perspective, the widespread adoption of electric light occurred before an understanding of circadian biology. The effects of what we now know to be a major change for circadian biology were simply not considered. It is essential that we learn about the effects of modern technology on the brain and health, so that we might appropriately manage them.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Navara KJ, Nelson RJ. The dark side of light at night: physiological, epidemiological, and ecological consequences. *J Pineal Res* 2007; **43**: 215–224.
2 Rajaratnam SM, Arendt J. Health in a 24-h society. *Lancet* 2001; **358**: 999–1005.
3 Karatsoreos IN, McEwen BS. Psychobiological allostasis: resistance, resilience and vulnerability. *Trends Cogn Sci* 2011; **15**: 576–584.
4 Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J Affect Disord* 1993; **29**: 85–96.
5 Schmidt TM, Chen SK, Hattar S. Intrinsically photosensitive retinal ganglion cells: many subtypes, diverse functions. *Trends Neurosci* 2011; **34**: 572–580.
6 Brainard GC, Hanifin JP, Greeson JM, Byrne B, Glickman G, Gerner E *et al.* Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci* 2001; **21**: 6405–6412.
7 Pauley SM. Lighting for the human circadian clock: recent research indicates that lighting has become a public health issue. *Med Hypotheses* 2004; **63**: 588–596.
8 Albrecht U, Sun ZS, Eichele G, Lee CC. A differential response of two putative mammalian circadian regulators, mper1 and mper2, to light. *Cell* 1997; **91**: 1055–1064.
9 Caldelas I, Poirel VJ, Sicard B, Pevet P, Challet E. Circadian profile and photic regulation of clock genes in the suprachiasmatic nucleus of a diurnal mammal *Arvicanthis ansorgei*. *Neuroscience* 2003; **116**: 583–591.
10 Hardeland R, Madrid JA, Tan DX, Reiter RJ. Melatonin, the circadian multioscillator system and health: the need for detailed analyses of peripheral melatonin signaling. *J Pineal Res* 2012; **52**: 139–166.
11 Brainard GC, Lewy AJ, Menaker M, Fredrickson RH, Miller LS, Weleber RG *et al.* Dose–response relationship between light irradiance and the suppression of plasma melatonin in human volunteers. *Brain Res* 1988; **454**: 212–218.
12 Brainard GC, Richardson BA, Petterborg LJ, Reiter RJ. The effect of different light intensities on pineal melatonin content. *Brain Res* 1982; **233**: 75–81.
13 von Gall C, Garabette ML, Kell CA, Frenzel S, Dehghani F, Schumm-Draeger PM *et al.* Rhythmic gene expression in pituitary depends on heterologous sensitization by the neurohormone melatonin. *Nat Neurosci* 2002; **5**: 234–238.
14 von Gall C, Weaver DR, Moek J, Jilg A, Stehle JH, Korf HW. Melatonin plays a crucial role in the regulation of rhythmic clock gene expression in the mouse pars tuberalis. *Ann N Y Acad Sci* 2005; **1040**: 508–511.
15 Bunney WE, Bunney BG. Molecular clock genes in man and lower animals: possible implications for circadian abnormalities in depression. *Neuropsychopharmacology* 2000; **22**: 335–345.
16 McClung CA. Circadian genes, rhythms and the biology of mood disorders. *Pharmacol Ther* 2007; **114**: 222–232.
17 McClung CA. Circadian rhythms and mood regulation: insights from pre-clinical models. *Eur Neuropsychopharmacol* 2011; **21**(Suppl 4): S683–S693.
18 Rosen LN, Targum SD, Terman M, Bryant MJ, Hoffman H, Kasper SF *et al.* Prevalence of seasonal affective disorder at four latitudes. *Psychiatry Res* 1990; **31**: 131–144.
19 Glickman G, Byrne B, Pineda C, Hauck WW, Brainard GC. Light therapy for seasonal affective disorder with blue narrow-band light-emitting diodes (LEDs). *Biol Psychiatry* 2006; **59**: 502–507.
20 Workman JL, Nelson RJ. Potential animal models of seasonal affective disorder. *Neurosci Biobehav Rev* 2011; **35**: 669–679.
21 Workman JL, Manny N, Walton JC, Nelson RJ. Short day lengths alter stress and depressive-like responses, and hippocampal morphology in Siberian hamsters. *Horm Behav* 2011; **60**: 520–528.
22 Ashkenazy T, Einat H, Kronfeld-Schor N. We are in the dark here: induction of depression- and anxiety-like behaviours in the diurnal fat sand rat, by short daylight or melatonin injections. *Int J Neuropsychopharmacol* 2009; **12**: 83–93.
23 Ashkenazy-Frolinger T, Kronfeld-Schor N, Juetten J, Einat H. It is darkness and not light: depression-like behaviors of diurnal unstriped Nile grass rats maintained under a short photoperiod schedule. *J Neurosci Methods* 2010; **186**: 165–170.
24 Ashkenazy T, Einat H, Kronfeld-Schor N. Effects of bright light treatment on depression- and anxiety-like behaviors of diurnal rodents maintained on a short daylight schedule. *Behav Brain Res* 2009; **201**: 343–346.
25 Ma WP, Cao J, Tian M, Cui MH, Han HL, Yang YX *et al.* Exposure to chronic constant light impairs spatial memory and influences long-term depression in rats. *Neurosci Res* 2007; **59**: 224–230.
26 Fujioka A, Fujioka T, Tsuruta R, Izumi T, Kasaoka S, Maekawa T. Effects of a constant light environment on hippocampal neurogenesis and memory in mice. *Neurosci Lett* 2011; **488**: 41–44.
27 Monje FJ, Cabatic M, Divisch I, Kim EJ, Herkner KR, Binder BR *et al.* Constant darkness induces IL-6-dependent depression-like behavior through the NF-kappaB signaling pathway. *J Neurosci* 2011; **31**: 9075–9083.
28 Gonzalez MM, Aston-Jones G. Light deprivation damages monoamine neurons and produces a depressive behavioral phenotype in rats. *Proc Natl Acad Sci USA* 2008; **105**: 4898–4903.
29 Cinzano P, Falchi F, Elvidge CD. The first World Atlas of the artificial night sky brightness. *Mon Not R Astron Soc* 2001; **328**: 689–707.
30 Brainard GC, Rollag MD, Hanifin JP. Photic regulation of melatonin in humans: ocular and neural signal transduction. *J Biol Rhythms* 1997; **12**: 537–546.
31 Healy D, Minors DS, Waterhouse JM. Shiftwork, helplessness and depression. *J Affect Disord* 1993; **29**: 17–25.
32 Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ *et al.* Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med* 2011; **68**: 154–162.
33 Noone P. Nightshift breast cancer, flour dust and blue-light risk. *Occup Med (Lond)* 2010; **60**: 499.
34 Dunn H, Anderson MA, Hill PD. Nighttime lighting in intensive care units. *Crit Care Nurse* 2010; **30**: 31–37.
35 Parthasarathy S, Tobin MJ. Sleep in the intensive care unit. *Intens Care Med* 2004; **30**: 197–206.
36 Bjorksten KS, Bjerregaard P, Kripke DF. Suicides in the midnight sun—a study of seasonality in suicides in West Greenland. *Psychiatry Res* 2005; **133**: 205–213.
37 Westman JA, Ferketich AK, Kauffman RM, MacEachern SN, Wilkins 3rd JR, Wilcox PP *et al.* Low cancer incidence rates in Ohio Amish. *Cancer Causes Control* 2010; **21**: 69–75.
38 Egeland JA, Hostetter AM. Amish Study, I: Affective disorders among the Amish, 1976–1980. *Am J Psychiatry* 1983; **140**: 56–61.
39 Tsuno N, Besset A, Ritchie K. Sleep and depression. *J Clin Psychiatry* 2005; **66**: 1254–1269.
40 Goodwin GM, Emsley R, Rembry S, Rouillon F. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; **70**: 1128–1137.
41 Kennedy SH, Rizvi SJ. Agomelatine in the treatment of major depressive disorder: potential for clinical effectiveness. *CNS Drugs* 2010; **24**: 479–499.
42 Crupi R, Mazzon E, Marino A, La Spada G, Bramanti P, Cuzzocrea S *et al.* Melatonin treatment mimics the antidepressant action in chronic corticosterone-treated mice. *J Pineal Res* 2010; **49**: 123–129.
43 Ramirez-Rodriguez G, Klempin F, Babu H, Benitez-King G, Kempermann G. Melatonin modulates cell survival of new neurons in the hippocampus of adult mice. *Neuropsychopharmacology* 2009; **34**: 2180–2191.
44 Kong X, Li X, Cai Z, Yang N, Liu Y, Shu J *et al.* Melatonin regulates the viability and differentiation of rat midbrain neural stem cells. *Cell Mol Neurobiol* 2008; **28**: 569–579.
45 Kuhlman SJ, Silver R, Le Sauter J, Bult-Ito A, McMahon DG. Phase resetting light pulses induce Per1 and persistent spike activity in a subpopulation of biological clock neurons. *J Neurosci* 2003; **23**: 1441–1450.
46 McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism* 2005; **54**: 20–23.

47 Yehuda R, Teicher MH, Trestman RL, Levengood RA, Siever LJ. Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. *Biol Psychiatry* 1996; **40**: 79–88.
48 Scott AJ, Monk TH, Brink LL. Shiftwork as a risk factor for depression: a pilot study. *Int J Occup Environ Health* 1997; **3**: S2–S9.
49 Czeisler CA, Johnson MP, Duffy JF, Brown EN, Ronda JM, Kronauer RE. Exposure to bright light and darkness to treat physiologic maladaptation to night work. *N Engl J Med* 1990; **322**: 1253–1259.
50 Katz G, Durst R, Zislin Y, Barel Y, Knobler HY. Psychiatric aspects of jet lag: review and hypothesis. *Med Hypotheses* 2001; **56**: 20–23.
51 Young DM. Psychiatric morbidity in travelers to Honolulu, Hawaii. *Compr Psychiatry* 1995; **36**: 224–228.
52 Cho K. Chronic 'jet lag' produces temporal lobe atrophy and spatial cognitive deficits. *Nat Neurosci* 2001; **4**: 567–568.
53 Ohta H, Yamazaki S, McMahon DG. Constant light desynchronizes mammalian clock neurons. *Nat Neurosci* 2005; **8**: 267–269.
54 Bedrosian TA, Weil ZM, Nelson RJ. Chronic dim light at night provokes reversible depression-like phenotype: possible role for TNF. *Mol Psychiatry* 2013 (in press).
55 Bedrosian TA, Galan A, Vaughn CA, Weil ZM, Nelson RJ. Light at night alters daily patterns of cortisol and clock proteins in female siberian hamsters. *J Neuroendocrinol* 2013 (in press).
56 Fonken LK, Finy MS, Walton JC, Weil ZM, Workman JL, Ross J *et al.* Influence of light at night on murine anxiety- and depressive-like responses. *Behav Brain Res* 2009; **205**: 349–354.
57 Fonken LK, Kitsmiller E, Smale L, Nelson RJ. Dim nighttime light impairs cognition and provokes depressive-like responses in a diurnal rodent. *J Biol Rhythms* 2012; **27**: 319–327.
58 Bedrosian TA, Fonken LK, Walton JC, Haim A, Nelson RJ. Dim light at night provokes depression-like behaviors and reduces CA1 dendritic spine density in female hamsters. *Psychoneuroendocrinology* 2011; **36**: 1062–1069.
59 Bedrosian TA, Weil ZM, Nelson RJ. Chronic citalopram treatment ameliorates depressive behavior associated with light at night. *Behav Neurosci* 2012; **126**: 654–658.
60 Frodl T, Meisenzahl EM, Zetzsche T, Born C, Groll C, Jager M *et al.* Hippocampal changes in patients with a first episode of major depression. *Am J Psychiatry* 2002; **159**: 1112–1118.
61 Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 1999; **19**: 5034–5043.
62 Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. *Am J Psychiatry* 2000; **157**: 115–118.
63 Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. *Neuron* 2002; **34**: 13–25.
64 Hajszan T, Dow A, Warner-Schmidt JL, Szigeti-Buck K, Sallam NL, Parducz A *et al.* Remodeling of hippocampal spine synapses in the rat learned helplessness model of depression. *Biol Psychiatry* 2009; **65**: 392–400.
65 Hajszan T, MacLusky NJ, Leranth C. Short-term treatment with the antidepressant fluoxetine triggers pyramidal dendritic spine synapse formation in rat hippocampus. *Eur J Neurosci* 2005; **21**: 1299–1303.
66 Hajszan T, Szigeti-Buck K, Sallam NL, Bober J, Parducz A, Maclusky NJ *et al.* Effects of estradiol on learned helplessness and associated remodeling of hippocampal spine synapses in female rats. *Biol Psychiatry* 2010; **67**: 168–174.
67 Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol Psychiatry* 2006; **59**: 1116–1127.
68 Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol Rev* 1998; **105**: 83–107.
69 Narasimamurthy R, Hatori M, Nayak SK, Liu F, Panda S, Verma IM. Circadian clock protein cryptochrome regulates the expression of proinflammatory cytokines. *Proc Natl Acad Sci USA* 2012; **109**: 12662–12667.
70 LeGates TA, Altimus CM, Wang H, Lee HK, Yang S, Zhao H *et al.* Aberrant light directly impairs mood and learning through melanopsin-expressing neurons. *Nature* 2012; **491**: 594–598.
71 Hattar S, Kumar M, Park A, Tong P, Tung J, Yau KW *et al.* Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *J Comp Neurol* 2006; **497**: 326–349.
72 Bedrosian TA, Vaughn CA, Galan A, Weil ZM, Nelson RJ. *Role of melatonin in depressive-like behaviors provoked by chronic light at night*. Society for Neuroscience Annual Meeting, 2012, New Orleansp. 94.01.
73 Compton WM, Conway KP, Stinson FS, Grant BF. Changes in the prevalence of major depression and comorbid substance use disorders in the United States between 1991–1992 and 2001–2002. *Am J Psychiatry 2006* **163**: 2141–2147.
74 Simon GE, VonKorff M. Reevaluation of secular trends in depression rates. *Am J Epidemiol* 1992; **135**: 1411–1422.
75 Obayashi K, Saeki K, Iwamoto J, Okamoto N, Tomioka K, Nezu S *et al.* Exposure to light at night, nocturnal urinary melatonin excretion, and obesity/dyslipidemia in the elderly: a cross-sectional analysis of the HEIJO-KYO study. *J Clin Endocrinol Metab* 2013; **98**: 337–344.