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Review article

# Light as a modulator of emotion and cognition: Lessons learned from studying a diurnal rodent

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ABSTRACT

Light profoundly affects the behavior and physiology of almost all animals, including humans. One such effect in humans is that the level of illumination during the day positively contributes to affective well-being and cognitive function. However, the neural mechanisms underlying the effects of daytime light intensity on affect and cognition are poorly understood. One barrier for progress in this area is that almost all laboratory animal models studied are nocturnal. There are substantial differences in how light affects nocturnal and diurnal species, e.g., light induces sleep in nocturnal mammals but wakefulness in diurnal ones, like humans. Therefore, the mechanisms through which light modulates affect and cognition must differ between the chronotypes. To further understand the neural pathways mediating how ambient light modulates affect and cognition, our recent work has developed a diurnal rodent model, the Nile grass rat (*Arvicanthis niloticus*), in which daytime light intensity is chronically manipulated in grass rats housed under the same 12:12 hour light/dark cycle. This simulates lighting conditions during summer-like bright sunny days vs. winter-like dim cloudy days. Our work has revealed that chronic dim daylight intensity results in higher depression- and anxiety-like behaviors, as well as impaired spatial learning and memory. Furthermore, we have found that hypothalamic orexin is a mediator of these effects. A better understanding of how changes in daytime light intensity impinge upon the neural substrates involved in affect and cognition will lead to novel preventive and therapeutic strategies for seasonal affective disorder, as well as for non-seasonal emotional or cognitive impairments associated with light deficiency.

## 1. Introduction

Light is a highly salient environmental factor influencing the brain and behavior beyond its role in visual perception. In mammalian species including humans, the so-called non-image forming effects of light include entraining circadian rhythms, mediating pupillary reflexes, regulating peripheral physiological events, promoting alertness or arousal, and modulating affect and cognition (Foster and Hankins, 2002; Fu et al., 2005). The daily light/dark cycle is the most reliable and predictable cue to entrain the circadian system (Daan and Aschoff, 2001). This system coordinates daily rhythms in our bodily functions to ensure that the activities among the various tissues and organs are synchronized with each other and with the day/night or light/dark cycles (Hastings et al., 2003).

While the illuminance necessary for entrainment of circadian rhythms varies among species, for humans, light as low as 120 lx is sufficient (Zeitzer et al., 2000). Light in our natural environment is much brighter, though, with examples being > 1000 lx in a typical retail store or ~100,000 lx outside on a bright sunny midday (Turner et al., 2010). Such different levels of illumination during the day have been found to influence human behavior and physiology. Compared to low daytime light intensity, bright illumination during the day increases arousal and enhances attention (Altimus et al., 2008; Ruger et al., 2006), activates digestive activity (Lee et al., 2001; Sone et al., 2003), suppresses plasma cortisol levels (Jung et al., 2010), and increases the nocturnal rise of melatonin (Park and Tokura, 1999). Furthermore, for patients that recently underwent spinal surgery, more sunlight in their hospital rooms decreased their pain and analgesic use (Walch et al., 2005), and heart attack patients in sunny hospital rooms have relatively shorter hospital stays and higher survival rates (Beauchemin and Hays, 1998). As will be discussed below as the focus of this review, brighter daytime illumination has also been found to have positive effects on affective well-being and cognitive function in humans, while insufficient light exposure during the day can lead to affective disorders and cognitive impairments.

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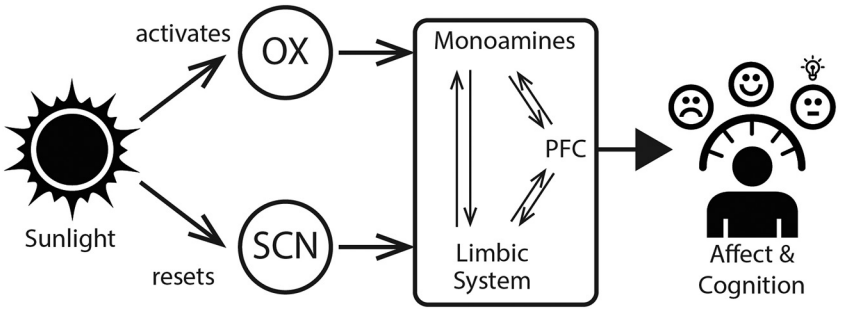


**Fig. 1.** Hypothetical model showing how light modulates affect (as well as cognition) through both circadian and non-circadian systems. Light resets the principal circadian clock located in the suprachiasmatic nucleus (SCN) of both diurnal and nocturnal mammals. Light activation of the orexinergic system (OX) is unique to diurnal mammals and, thus, can only be studied in a diurnal model such as Nile grass rats. Both systems regulate functions of the monoaminergic system, subcortical regions of the limbic system including the hippocampus, and the prefrontal cortex (PFC) – all of which are involved in regulating affect and cognition.

## 2. Daylight modulates affect and cognition in humans

The impact of light on our affective state is best exemplified by seasonal affective disorder (SAD) and the effectiveness of bright light therapy in preventing, or at least alleviating, many of its symptoms (Lam et al., 2006; Nussbaumer et al., 2015; Rosenthal et al., 1984; Terman and Terman, 2005). SAD is a major depressive disorder occurring with a seasonal pattern that affects millions of Americans every year (Howland, 2009). Affected individuals experience regularly recurring episodes of depression and anxiety each fall and winter, followed by spontaneous remission in spring and summer (Rosenthal et al., 1984). Bright light therapy is effective in alleviating the symptoms of SAD, suggesting that the cause of this disorder lies in the seasonal fluctuation in lighting condition. In addition to SAD, bright light therapy has been successfully used to treat non-seasonal depression, suggesting modulatory effects of light on mood regardless of the season (Even et al., 2008; Golden et al., 2005; Tuunainen et al., 2004). A recent study showed that for hospitalized depression patients, those staying in southeast-facing rooms recovered much faster compared those who stayed in northwest-facing rooms (average of 29.2 ± 26.8 versus 58.8 ± 42.0 days to recover) (Gbyl et al., 2016). The only factor that could account for the speedy recovery in southeast-facing patients is that their rooms were much brighter compared to those in the other side of the building, and the difference in recovery time was up to 20-fold at any given time of the year. A group of retinal ganglion cells containing the photoreceptor molecule, melanopsin, play a critical role in detecting light intensity and mediating the non-image forming effects of light (Hattar et al., 2003). Indeed, homozygosity for missense single-nucleotide polymorphisms in the melanopsin gene increases the risk of SAD by over 500%, suggesting deficits in non-visual pathways from the retina as risk factors that may predispose some individuals to the disorder (Roecklein et al., 2009). Retinal disease that leads to visual impairment is also consistently associated with depression and anxiety (Augustin et al., 2007; Ribeiro et al., 2015). Although in the latter cases the high prevalence of depression and anxiety could very reasonably be secondary to the visual impairments, the direct impact of diminished non-image forming photic stimulation to the brain should not be underestimated.

In addition to depression and anxiety, SAD patients also experience cognitive impairments including slower cognitive processing as well as impaired working and spatial memory (O'Brien et al., 1993; Sullivan and Payne, 2007). Seasonal effects on cognitive function have also been documented in non-clinical populations. A recent fMRI study revealed seasonal fluctuation in brain activity during cognitive tasks, such that the brain responses to a sustained attention task were highest in summer and lowest in winter, while the responses to working memory were highest in the fall and lowest in spring (Meyer et al., 2016). The impact of light on cognitive function has also been documented in human populations independent of season. As examples, brighter illumination in the classroom enhances math and reading performance of elementary school students (Barkmann et al., 2012; Heschong, 2002; Heschong et al., 2002; Mott et al., 2012), bright office lighting increases performance of adults in the workplace (Baron et al., 1992; Mills et al., 2007; Viola et al., 2008), and bright light therapy improves cognition in mild/early-stage dementia in some studies (Forbes et al., 2009; Riemersma-van der Lek et al., 2008; Yamadera et al., 2000).

## 3. Studying a diurnal animal is essential for elucidating the mechanisms responsible for daylight's modulation of human affect and cognition

Evidence from the literature on both clinical and non-clinical populations summarized above has firmly established that environmental lighting condition is an important modulator of mood and cognition in humans. However, how bright daylight produces its positive effects on affective and cognitive outcomes is poorly understood, and research in this area has been greatly hindered by a lack of an appropriate animal to study such questions. In contrast to humans that are diurnal and, thus, most active during the day, the most commonly studied laboratory rodents including mice or rats are nocturnal and active at night. Although light entrains or resets circadian rhythms in a manner that is very similar or even the same between nocturnal and diurnal mammals, the circadian-independent direct effects of light on the brain and behavior are very different (Challet, 2007; Minors et al., 1991; Smale et al., 2003; Yan et al., 2018). Most saliently, light increases physical activity and promotes arousal in diurnal mammals, while light inhibits activity and promotes sleep in nocturnal ones (Redlin, 2001). Therefore, studying a diurnal animal is absolutely essential to fully understand the impact of ambient light on the human brain, behavior, and physiology through light's circadian-dependent and circadian-independent mechanisms (Fig. 1).

A small number of diurnal rodent species are available to study in laboratory settings and include degus (*Octodon degus*), Mongolian gerbils (*Meriones unguiculatus*), and Nile grass rats (*Arvicanthis niloticus*). Of these diurnal rodents, Nile grass rats have the highest diurnality index at 87%, i.e., the percentage of daily activity occurring during the daytime (Refinetti, 2008). Work from our group discussed below utilizing male Nile grass rats (and very recently also involving females) has established that daytime lighting condition influences their emotional and cognitive behaviors in a way similar to that seen in humans, such that insufficient light exposure during the day leads to increased depression- and anxiety-like behaviors, as well as impaired spatial learning and memory.

## 4. Daytime light deficiency impairs affective behaviors and cognition in grass rats in ways analogous to those seen in humans

Depression-like behaviors have been consistently observed by our group and others in diurnal grass rats housed in winter-like lighting conditions involving short day-length of either 5:19 or 8:16 hour light/dark (LD) cycle (Ashkenazy-Frolinger et al., 2009; Leach et al., 2013b), or involving low light intensity even if the animals are maintained on a 12:12 hour LD cycle (Leach et al., 2013a). These results clearly demonstrate that not only does winter-like short day length, but also winter-like low daylight intensity, contributes to the behavioral deficits. The depression-like behavior displayed by grass rats housed under

winter-like lighting conditions also strongly supports the face validity of the diurnal grass rat as a model of SAD. Following these initial findings, we focused our investigation using the low light intensity paradigm instead of the short photoperiod due to the fact that it is much more relevant to the seasonal changes in light intensity experienced by humans. Importantly, because most humans around the globe use artificial lights, the duration of daily light exposure we experience across seasons does not fluctuate nearly as much as the quality/intensity of light. In a study monitoring light exposure in a group of subjects at the 45° N latitude (Quebec, Canada) where the natural day-length fluctuates between 8 and 16 hours across the year, the total duration of light exposure experienced by the subjects was not significantly different between winter and summer (14.6 ± 1.2 vs. 14.9 ± 1.5 h). However, the duration of light above 1000 lx was greatly reduced in winter compared to summer (2.6 ± 1.2 vs. 0.4 ± 0.3 h) (Hebert et al., 1998). Therefore, the change in daylight intensity over the seasons is a more salient factor than daylight duration for driving seasonality in modern humans.

To assess the effects of daytime light intensity on affective and cognitive responses, we housed diurnal grass rats under a 12:12 hour LD condition with either bright (1000 lx, brLD) or dim light (50 lx, dimLD) during the day, thus resembling the lighting conditions that many of us experience in summer or winter, respectively. It should be noted that the light exposure is voluntary because the animals can always avoid the light by hiding in a PVC tube provided as enrichment in their home cages. Even so, we have often observed that the animals in the brLD condition stand on top of the PVC tube to be closer to the light source, suggesting that the light at 1000 lx (which is higher than the standard for most laboratory rodent animal facilities) is not aversive but rather desirable for the grass rats. Following 4 weeks in each lighting condition, the animals underwent behavioral testing. Consistent to what has been observed in humans suffering with SAD, compared to the control group housed in the summer-like brLD condition, grass rats housed in winter-like dimLD condition showed increased depression- and anxiety-like behaviors. Depression-like behaviors were assessed in the classic forced swim test (FST) and sweet solution preference (SSP) test (Leach et al., 2013a). In the FST, the dimLD animals showed longer immobility and less climbing/escaping, indicating more behavioral despair (Fig. 2). In a SSP test that permits free ingestion of 1% saccharin and tap water, the SSP of dimLD animals was significantly lower than that of brLD animals, indicating anhedonia. Anxiety-like behaviors were assessed in open field and marble burying tests (Ikeno et al., 2016). In the open field test, animals in the dimLD group had fewer center entries and spent less time at the center of the testing arena (Fig. 3). In the marble burying test, the dimLD group buried twice many marbles, compared to the brLD group. The behavioral responses in both tests reveal anxiety-like phenotype of animals housed in dimLD.

We also examined the effects of daytime light intensity on spatial learning and memory using the hippocampal-dependent Morris water maze (MWM) task (Soler et al., 2018). Lighting condition affected the latency for the animals to locate the platform across the training days (2 trials/day for 5 days), with the effect being significant only for trial 1 (with 24-hours between trials), but not trial 2 (30 seconds after trial 1), indicating that retention of the memory for the platform location was impaired in the dimLD animals after a 24-hour interval, but that their working memory was intact (Fig. 4). During the 60-second probe test administered 24 h after the last training day, the dimLD animals spent ~15 s of the testing period in the goal quadrant, which is at chance level, indicating impairments of spatial memory (Fig. 4). It is noteworthy that there was no difference in thigmotaxis (time spent swimming next to the wall and often used as a measure of anxiety) between the two groups during the probe test. This finding seems inconsistent with the anxiety-like phenotype of dimLD animals we observed in previous studies, which included increased thigmotaxis by dimLD animals during open field and forced swim tests (Deats et al., 2014; Ikeno et al., 2016). The different behavioral response could be due to the fact that: 1) the pool for the MWM task is much larger than the open field arena or the pool used for the forced swim testing, and 2) the MWM task is goal-oriented and the animals are motivated to find the platform hidden near the center of the pool, so the testing conditions are biased against the display of thigmotaxic behavior.

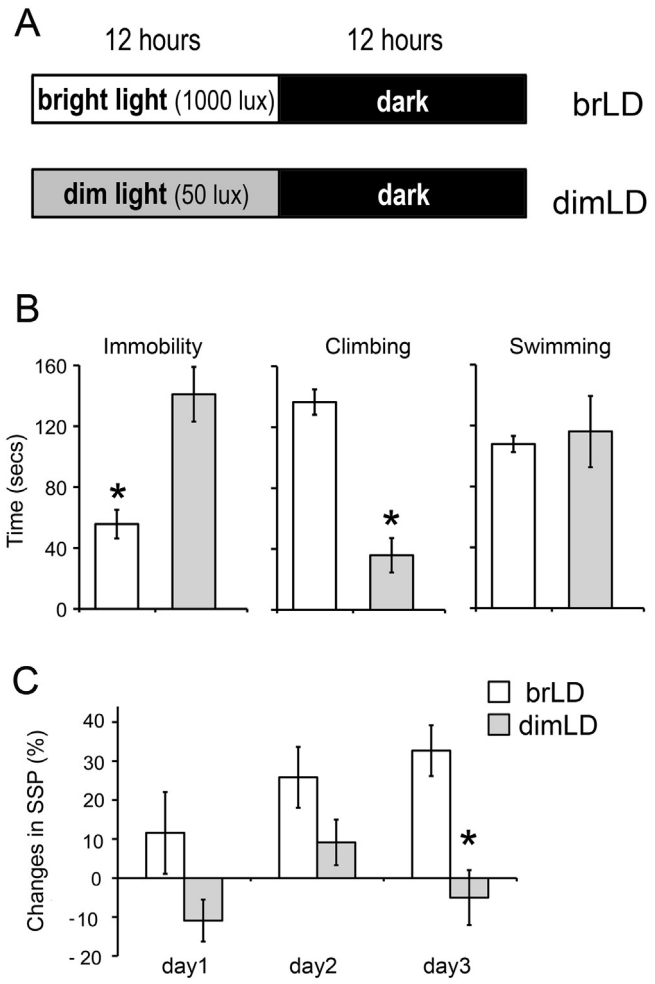


**Fig. 2.** Daytime dim light housing leads to depression-like behavioral responses. A. Diagrams depicting the bright light:dark (brLD) and dim light:dark (dimLD) conditions used to study behavior in Nile grass rats. B. Bar graphs show the duration of immobility, escaping, and swimming by grass rats during forced swim tests (FST), indicating behavioral despair in the animals housed in dimLD. C. The changes in preference for saccharine solution by grass rats in sweet solution preference (SSP) tests. Animals in brLD showed a steady increase in their SSP, while dimLD group did not show an increase of SSP over 3 days of exposure, indicating anhedonia. Results are displayed as mean ± SEM. * indicates $p < 0.05$.
(B and C are modified from Fig. 1 in Leach et al., 2013a).

## 5. The circadian system is not responsible for the behavioral impairments seen in grass rats housed in winter-like dimLD conditions

The current prevailing theory on the etiology of SAD continues to be the phase-shifting hypothesis, which proposes that the episodes of depression are caused by misalignments between one's circadian rhythm and habitual sleep time (Lewy et al., 2007). The clinical practice of using light therapy is based on this theory (Lewy, 2009; Terman and Terman, 2005), which is derived from the fact that light is undoubtedly the most salient cue for resetting circadian rhythms (Daan and Aschoff, 2001). However, the light intensity required for effective light therapy in humans (> 5000 lx (Terman et al., 1996; Terman and Terman,

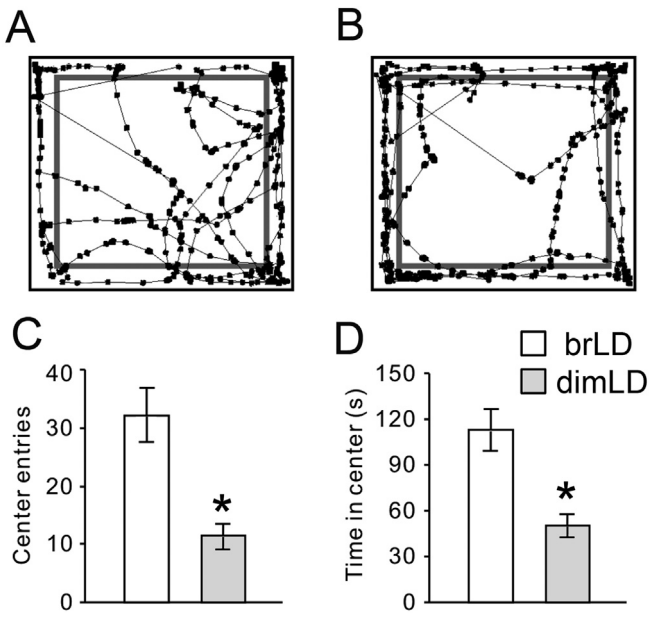


**Fig. 3.** Daytime dim light housing leads to increased anxiety-like behavior. (A, B) Representative tracks in an open field by grass rats housed in the brLD (A) and dimLD (B) conditions. The center/perimeter boundaries are shown in grey lines. (C) Total number of center entries. (D) Total time spent in the center. Results are shown as mean ± SEM. *$p < 0.01$.
(Adapted from Fig. 1 in Ikeno et al., 2016 with permission).

2005)) is known to greatly exceed that needed to shift our circadian rhythms (120 lx (Zeitzer et al., 2000)). Thus, the role that the circadian system plays in SAD is not completely clear.

To determine if circadian rhythm disruption underlies the behavioral impairments seen in our grass rats housed under dimLD conditions, we compared their daily rhythms in locomotor activity to animals in the brLD condition (Fig. 5A; Leach et al., 2013a). There were no significant differences between the two conditions in terms of the animals' total daily activity, day/night activity ratio, and entrainment phase angle (i.e., the activity onset and offset time in reference to lights on and off, respectively). The only significant difference found was in the entrainment stability measured by the activity offset, with greater variability in the timing of the end point of daily activity for animals housed in dimLD compared to those in brLD. However, there was no difference when the entrainment stability was assessed based on activity onset time. Therefore, the analysis of locomotor activity revealed no major differences in daily rhythms that could have contributed to the behavioral impairments in the dimLD group (Leach et al., 2013a).

The grass rat model of SAD also allowed us to directly examine the functioning of circadian oscillators, including the principal brain clock within the suprachiasmatic nucleus (SCN). We examined the expression of the protein product of the canonic clock gene PER2 in the SCN across a daily cycle in grass rats housed in brLD or dimLD and found no significant differences between the groups (Fig. 5B, Ikeno and Yan, unpublished results).

It is well established that circadian rhythm disruption is a causal factor for mood disorders and cognitive impairments (Evans and Davidson, 2013; McClung, 2011; Wright et al., 2012). However, the rather subtle differences in circadian rhythms between the brLD and dimLD grass rats, and the much higher intensity required for the antidepressant effects of light therapy than that for circadian entrainment in humans (i.e. 5000 vs. 120 lx), collectively suggest that there are mechanisms in addition to - and more importantly independent of - circadian disruption that contribute to the behavioral deficits caused by daytime light deficiency.

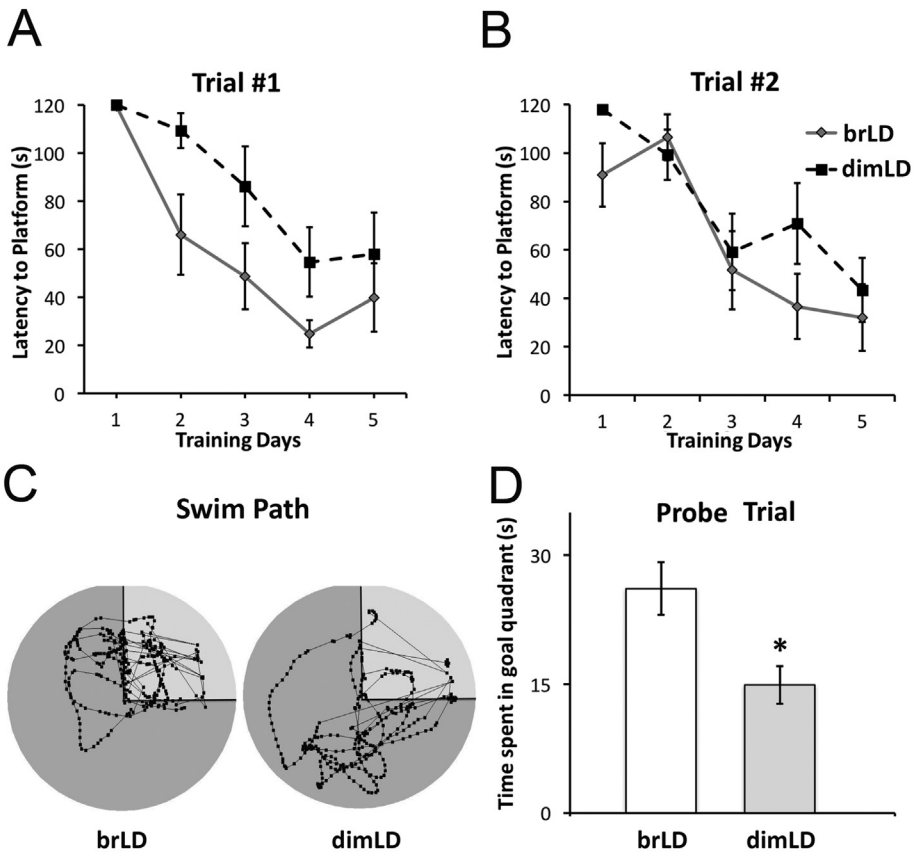


**Fig. 4.** Impaired MWM performance of grass rats housed in dimLD compared to those in brLD condition. (A) Latency of animals to locate the platform during trial 1 (24-hour delay) over the five training days. Grass rats housed in brLD were able to locate the platform significantly faster in the than those housed in dimLD. (B) Latency of animals to locate the platform during trial 2 (30-second delay); there were no significant differences between the two groups. (C) Representative track plots of a grass rat in each lighting condition during the probe trial (with goal quadrant highlighted). (D) Grass rats housed in brLD nearly spent twice as much time searching for the platform in the goal quadrant in the probe test when compared to grass rats in the dimLD group. *$p < 0.05$.
(Adapted from Fig. 1 in Soler et al., 2018 with permission).

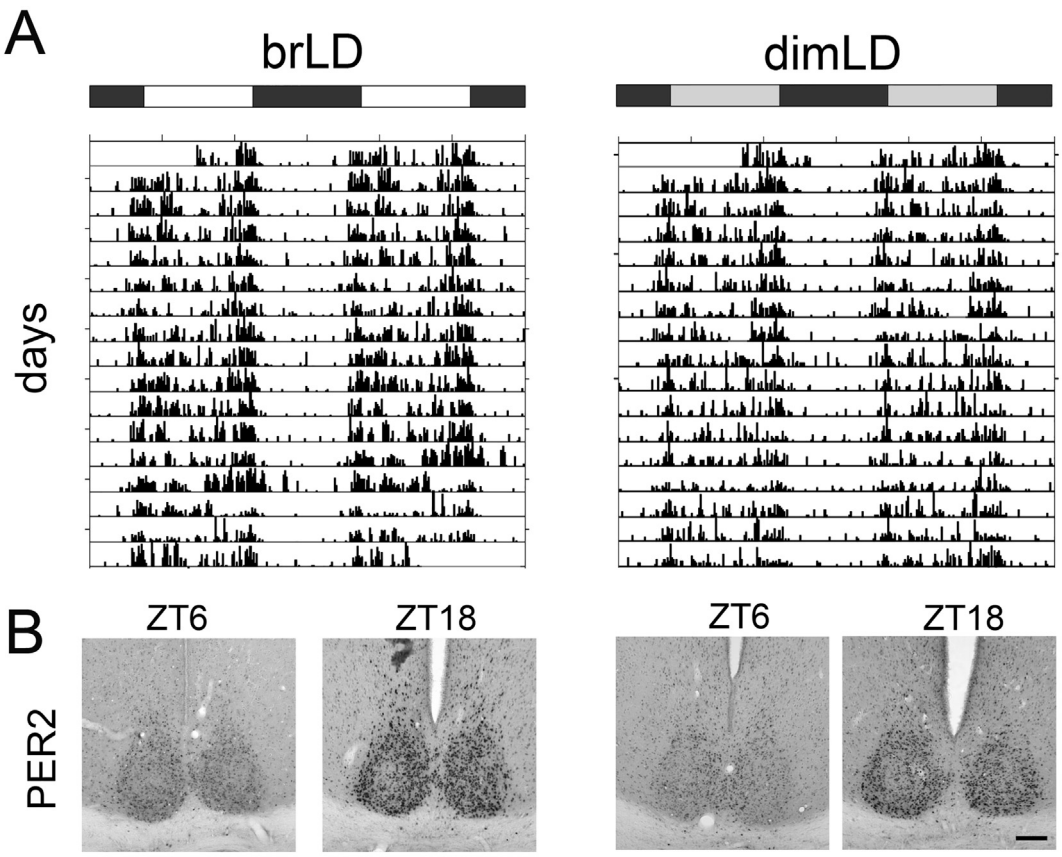


**Fig. 5.** Daily rhythms in locomotor activity and expression of the clock protein PER2 in the SCN are comparable between grass rats housed in brLD or dimLD conditions. (A) Actograms depict representative daily activity of a grass rat housed in each condition over two weeks. Daily activity is double-blotted so each horizontal line shows activity over two days. Each vertical bar shows the amount of activity over a 10-minute bin. In both conditions, the majority of activity occurred during daytime. (B) PER2 immunoreactivity in the SCN. Scale bar, 100 μm.
(Adapted from Fig. 3 in Leach et al., 2013a).

## 6. Does the orexin system underlie the behavioral deficits caused by daytime light deficiency?

Orexin, also known as hypocretin, has two isoforms (orexin A and orexin B) that have been implicated in many important physiological functions including wakefulness, energy homeostasis, reward, emotion, and cognition (Gerashchenko and Shiromani, 2004; Tsujino and Sakurai, 2009). The sequence and structure of orexin peptides are well conserved across mammals such as mice, rats, dogs, pigs and humans (Sakurai, 2005). Mood and anxiety disorders are prevalent in narcoleptic patients that have diminished central orexin levels (Fortuyn et al., 2010; Ohayon, 2013). Lower orexin levels in cerebrospinal fluid have also been reported in patients suffering from major depressive disorder or comorbid depression and anxiety ((Brundin et al., 2007a,b, 2009; Johnson et al., 2010; Rotter et al., 2011) also see (Schmidt et al., 2011)). In laboratory animal models of depression, reduced brain orexin peptide content and a reduced number or size of orexin neurons have been reported (Allard et al., 2004; Nocjar et al., 2012). There is also evidence for the involvement of the orexinergic system in cognition. Dysfunction in the orexin system has been implicated in dementia and in cognitive decline in post-stroke patients (Song et al., 2015; Wennstrom et al., 2012). In nocturnal rodents, orexin has been shown to modulate hippocampal-dependent spatial learning (Sil'kis, 2013). Orexin A also reverses the impaired spatial learning and memory in a mouse epilepsy model (Zhao et al., 2014), and improves retention in avoidance learning (Jaeger et al., 2002). There are two types of G-protein-coupled receptors that bind orexin. Type 1 receptors (OX1R) show higher affinity for orexin A, while type 2 receptors (OX2R) have similar affinity to both orexin A and B (Sakurai et al., 1998). Administering a selective OX1R antagonist into the CA1 impairs learning in the MWM task (Akbari et al., 2006, 2007), suggesting that OX1R-mediated signaling in CA1 is involved in spatial learning.

Most orexin-containing neurons in the brain are localized in the lateral hypothalamus of humans (Aziz et al., 2008; Thannickal et al., 2009), as well as in diurnal and nocturnal rodents (Donlin et al., 2014; Nixon and Smale, 2007). In both laboratory rats and grass rats, there are direct retinal projections to the lateral hypothalamus where most orexinergic cells are found (Gaillard et al., 2013; Johnson et al., 1988; Leak and Moore, 1997). These hypothalamic orexin neurons also receive retinal input indirectly through the suprachiasmatic nucleus in both species (Deurveilher and Semba, 2005; Schwartz et al., 2011). In diurnal grass rats, we have found that acute light exposure activates orexin neurons (as revealed by increased Fos expression), indicating that these cells are light responsive (Adidharma et al., 2012). We then assessed the effects of daytime illumination level on the orexin neurons. Compared to brDL grass rats housed for 4 weeks in the bright daylight conditions, the dimDL animals had fewer orexin-ir cells in the hypothalamus and lower orexin-ir fiber density in the midbrain dorsal raphe nucleus (Deats et al., 2014), suggesting decreased central orexin levels and attenuated orexinergic output (Fig. 6). Furthermore, administering a selective OX1R antagonist to animals in the brLD condition increased their depression- and anxiety-like behaviors (Deats et al., 2014), suggesting that functioning orexin-OX1R pathways are critical for the absence of negative affective behaviors in grass rats.

Critically important for modulating depression, anxiety, learning and memory is that orexinergic cells project heavily to the prefrontal cortex, monoaminergic systems, and hippocampus in both nocturnal laboratory rats and diurnal grass rats (Nixon and Smale, 2007; Peyron

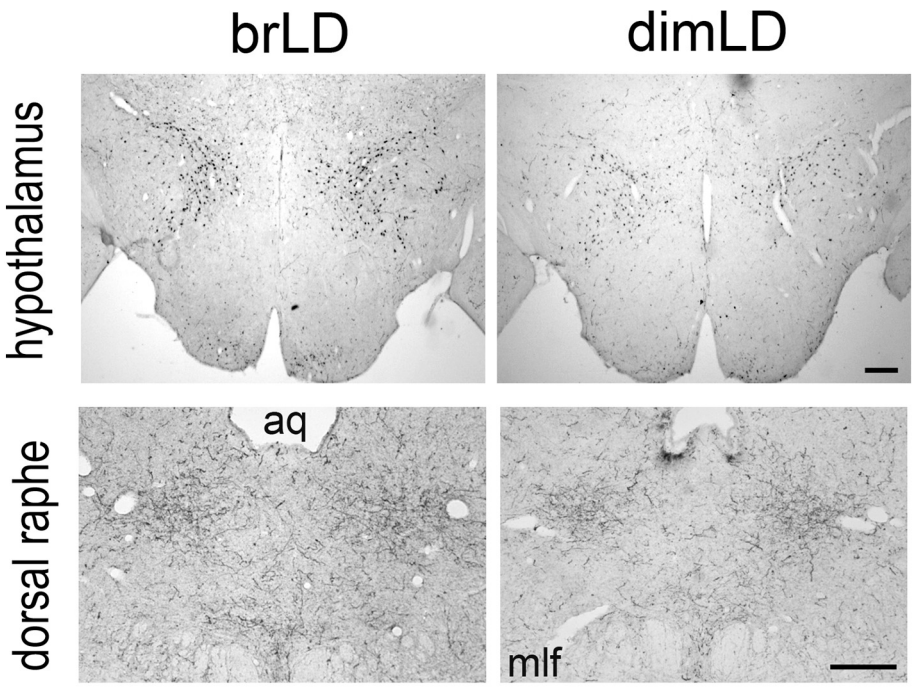


**Fig. 6.** Daytime dim light housing (dimLD) leads to attenuated orexin immunoreactivity in the hypothalamus (upper panel) and the dorsal raphe nucleus (lower panel) compared to daytime bright light housing (brLD). aq, cerebral aqueduct; mlf, medial longitudinal fasciculus. Scale bars = 250 μm. (Modified from Figs. 1 and 2 in Deats et al., 2014 with permission).

et al., 1998; Fig. 1). Using diurnal grass rats, we have investigated the effects of daytime light intensity on some targets of the hypothalamic orexin cells, to explore the potential downstream pathways from light via orexin neurons in mediating the effects of daytime illumination on affect and cognition.

### 6.1. The dorsal raphe nucleus (DRN)

Orexin cells project heavily to central monoaminergic systems including the serotonin (5-HT)-rich DRN (Nixon and Smale, 2007; Peyron et al., 1998), where it induces excitatory responses in 5-HTergic cells (Soffin et al., 2004) and stimulates local release of 5-HT (Tao et al., 2006). Dysfunction in the central 5-HT system has long been implicated in the pathophysiology of SAD. SAD patients in clinical remission will relapse following depletion of the 5-HT precursor, tryptophan (Kulikov and Popova, 2015; Lam et al., 2001; Levitan, 2007; Neumeister et al., 2001). There are also seasonal variations in the 5-HT system. In humans, hypothalamic 5-HT levels (Carlsson et al., 1980), 5-HT turnover as measured by its metabolite levels in cerebrospinal fluid (Brewerton et al., 1988; Luykx et al., 2013), and availability of 5-HT1A receptors in a variety of subcortical sites (Matheson et al., 2015) are lowest in winter, while 5-HT transporter binding potential in cortical and subcortical sites is highest in both fall and winter (Praschak-Rieder et al., 2008). It has also been shown that bright sunlight rapidly increases 5-HT production, which is correlated with the duration and intensity of light exposure (Lambert et al., 2002). In diurnal grass rats, we found that dimLD animals had fewer 5-HT-ir cells at middle and caudal levels of the DRN, and lower 5-HT-ir fiber density in the medial cingulate cortex, when compared to brLD animals (Leach et al., 2013a). This decrease in midbrain and frontocortical 5-HT cells and fibers in dimLD animals is consistent with our finding that bright light increases immediate-early gene activity in the grass rat DRN (Adidharma et al., 2012). Although a direct retinal projection to the dorsal raphe has been reported in many species including laboratory rats, degus, gerbils, tree shrews, and tufted capuchin monkeys (Fite and Janusonis, 2001; Fite et al., 1999; Frazao et al., 2008; Ren et al., 2013; Reuss and Fuchs, 2000; Shen and Semba, 1994), no direct retinal innervation of the DRN has been found in laboratory mice, ground squirrels, or grass rats (Gaillard et al., 2013; Hattar et al., 2006; Major et al., 2003; Morin and Studholme, 2014). Consistent with the anatomy, we have found that systemic injection of the selective OX1R antagonist, SB-334867, attenuates light-activated Fos expression in the DRN by almost 50%, suggesting that the light-induced activation of the DRN in grass rats is indirectly mediated by the OXA-OX1R pathway (Adidharma et al., 2012).

### 6.2. Hippocampus

The hippocampus has long been a focus of studies on learning and memory (Jarrard, 1993; Squire, 1992), and has also been implicated in depression (Campbell and Macqueen, 2004; MacQueen and Frodl, 2011) and anxiety (Bannerman et al., 2004; Shin and Liberzon, 2010). Orexinergic cells project directly to the hippocampus in both nocturnal laboratory rats and diurnal grass rats (Nixon and Smale, 2007; Peyron et al., 1998). Furthermore, orexin receptors are expressed in the hippocampus of both rodents (Ikeno and Yan, 2018; Marcus et al., 2001; Trivedi et al., 1998). In the grass rats, we examined hippocampal expression of the neurotrophic factor, BDNF, and CA1 dendritic spine density (Soler et al., 2018) and found a significant reduction in the number of hippocampal BDNF-ir cells in the dimLD condition that was specific to the CA1 subregion. This finding was confirmed by measurements of BDNF mRNA and protein using qPCR and Western blot, respectively. There was also a reduction in CA1 apical dendritic spine density in the dimLD group compared to brLD group. Interestingly, when a group of dimLD animals were transferred into the brLD condition for 4 weeks, both the BDNF expression and CA1 dendritic spine density rose. Hippocampal BDNF and spine density have been implicated in spatial learning and memory (Bekinschtein et al., 2008; Matsuzaki et al., 2004; Tsien et al., 1996) as well as in depression (Castren et al., 2007; Duman, 2002). Our findings revealed that daytime illumination modulates structural plasticity in the hippocampus, which likely contributes to the differential depression-like behaviors and spatial learning of grass rats housed in dim and bright days.

### 6.3. HPA axis

Dysregulation of the HPA axis has often been implicated in affective disorders (Belvederi Murri et al., 2016; Pariante and Lightman, 2008;

Zorn et al., 2017). Although we have found no differences between grass rats housed in brLD and dimLD conditions in their basal plasma corticosterone (CORT) at daytime or nighttime, nor in their adrenal gland weights, the dimLD group had relatively higher plasma CORT following an acute mild stressor (a marble-burying test (Ikeno et al., 2016)). The higher CORT levels in the dimLD group were accompanied by higher Fos immunoreactivity in the CA3 and dentate gyrus of the hippocampus, suggesting abnormal hippocampal regulation of the HPA axis in the dimLD animals. In support, we found that dimLD grass rats had higher hippocampal expression of the mRNAs for mineralocorticoid receptors (MR) at ZT2 and ZT14, and glucocorticoid receptors (GR) at ZT2, compared to that found in the brLD group. No such differences betwen groups in MR or GR mRNAs were found in the PVN (Ikeno et al., 2016). Because limiting light exposure via short photoperiod has previously been seen to increase hippocampal MR and GR expression in nocturnal rodents (Lance et al., 1998; Pyter et al., 2007), the upregulation in the hippocampus of the dimLD grass rats was unexpected. Higher hippocampal MR and GR expression would be expected to result in less initial CORT release and stronger negative feedback on the HPA axis in response to a stressor, rather than the higher plasma CORT we observed in the dimLD group. However, we measured CORT only at one time point (1 h) after the animals encountered the mild stressor. A complete time course of sampling plasma CORT from before the stress induction through complete recovery will be necessary to evaluate how changes in MR and GR mRNA are related to the HPA axis regulation in brDL and dimDL grass rats. Nonetheless, our results collectively suggest that the dimLD condition is associated with enhanced stress responding at multiple levels including in the animals' behavior, hormone secretion, and hippocampal gene expression.

## 7. Conclusions and future questions

Using the diurnal Nile grass rat, we have found that daytime light intensity level has significant impacts on affective behaviors and on spatial learning and memory. Brighter daytime illumination reduces depression- and anxiety-like behaviors and enhances spatial memory, while relatively dim light during the daytime leads to increased depression- and anxiety-like behaviors and impaired spatial memory. These behavioral responses observed in grass rats mirror what have been documented in humans, with bright light associated with a lack of negative affect and better cognitive performance. Thus, the grass rat provides a unique opportunity to reveal the neural mechanisms through which daytime light intensity modulates affect and cognition in humans. Current available data suggest that the hypothalamic orexin system is an important mediator of these lighting effects, by responding to changes in the level of daytime illumination and conveying such information to other brain regions involved in affective behaviors and spatial memory (Fig. 1). Light-induced activation of orexin neurons is unique for diurnal species (Adidharma et al., 2012) because in nocturnal rodents, orexin neurons are not activated by light (Mendoza et al., 2010) and instead are activated by darkness (Marston et al., 2008), which represents an arousal cue for these and other nocturnal animals. Interestingly, there are a handful of chronotype differences in the distribution of orexin receptors, especially OX1R, in brain regions implicated in sleep/wakefulness, affect, and cognition (Ikeno and Yan, 2018; Marcus et al., 2001; Trivedi et al., 1998). For instance, in the caudate putamen and ventral tuberomammillary nucleus, OX1R expression was detected in diurnal grass rats but not in nocturnal laboratory mice or rats; while in the medial division of the posteromedial bed nucleus of the stria terminalis OX1R was detected in mice but not in grass rats. These differences may eventually be found to underlie different roles for the OX1R in processing light in diurnal and nocturnal species.

Although our work has focused on the effects of differential light intensity, other parameters of ambient daylight including the duration of light exposure or the spectrum of light, are known to play a role in affective and cognitive behaviors in some diurnal and nocturnal rodents (Einat et al., 2006; Itzhacki et al., 2018; Leach et al., 2013a,b; Prendergast and Kay, 2008; Prendergast and Nelson, 2005; Pyter et al., 2005; Steinman et al., 2011), and these parameters will be explored in our future studies of grass rats. It should also be noted that the work discussed here is based on results obtained from male grass rats. We are currently investigating the effects of daytime light intensity in female grass rats, and the initial findings have suggested some intriguing sex differences. For instance, following the same housing condition in dimLD, the spatial memory deficits in female grass rats are even more severe than those found in males (Yan et al., 2017), and the effects of daytime light intensity on the levels orexin receptor expression also appear to be sex-specific in some brain regions (Tang et al., 2018).

In sum, the work from our group and others summarized in this review is a first step toward a better understanding of how light, via orexin, modulates affect and cognition in diurnal mammals. Such knowledge is essential for designing lighting environments that promote optimal affective and cognitive functioning, and for identifying risk factors and pharmacological targets for affective disorders and cognitive impairments, in humans.

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## Declarations of interest

None.

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