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Light modulates hippocampal function and spatial learning in a diurnal rodent species: A study using male nile grass rat (*Arvicanthis niloticus*)

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Abstract

The effects of light on cognitive function have been well-documented in human studies, with brighter illumination improving cognitive performance in school children, healthy adults, and patients in early stages of dementia. However, the underlying neural mechanisms are not well understood. The present study examined how ambient light affects hippocampal function using the diurnal Nile grass rats (*Arvicanthis niloticus*) as the animal model. Grass rats were housed in either a 12:12 h bright light–dark (brLD, 1,000 lux) or dim light-dark (dimLD, 50 lux) cycle. After 4 weeks, the dimLD group showed impaired spatial memory in the Morris Water Maze (MWM) task. The impairment in their MWM performance were reversed when the dimLD group were transferred to the brLD condition for another 4 weeks. The results suggest that lighting conditions influence cognitive function of grass rats in a way similar to that observed in humans, such that bright light is beneficial over dim light for cognitive performance. In addition to the behavioral changes, grass rats in the dimLD condition exhibited reduced expression of brain-derived neurotrophic factor (BDNF) in the hippocampus, most notably in the CA1 subregion. There was also a reduction in dendritic spine density in CA1 apical dendrites in dimLD as compared to the brLD group, and the reduction was mostly in the number of mushroom and stubby spines. When dimLD animals were transferred to the brLD condition for 4 weeks, the hippocampal BDNF and dendritic spine density significantly increased. The results illustrate that not only does light intensity affect cognitive performance, but that it also impacts hippocampal structural plasticity. These studies serve as a starting point to further understand how ambient light modulates neuronal and cognitive functions in diurnal species. A mechanistic understanding of the effects of light on cognition can help to identify risk factors for cognitive decline and contribute to the development of more effective prevention and treatment of cognitive impairment in clinical populations.

KEYWORDS

light, hippocampus, diurnal, synaptic plasticity, brain-derived neurotrophic factor

1 | INTRODUCTION

Environmental lighting conditions influence a vast array of physiological and behavioral processes in humans, i.e., circadian rhythms, alertness/arousal, as well as mood and cognition (Chellappa, Gordijn, & Cajochen, 2011; LeGates, Fernandez, & Hattar, 2014; Vandewalle, Maquet, & Dijk, 2009). The effects of light in regulating cognitive processes have been documented across diverse populations, with brighter illumination yielding improved cognitive performance. For example, brighter illumination in the classroom enhances the performance of elementary school students in math and reading (Barkmann, Wessolowski, & Schulte-Markwort, 2012; Heschong, 2002; Heschong et al., 2002; Mott, Robinson, Walden, Bernette, & Rutherford, 2012); bright office lighting improves the performance of adults in the work environment (Baron, Rea, & Daniels, 1992; Mills, Tomkins, & Schlangen, 2007; Viola, James, Schlangen, & Dijk, 2008) and bright light therapy has been shown to attenuate cognitive deterioration in mild/early-stage dementia (Forbes et al., 2009; Riemersma-van der Lek et al., 2008; Yamadera,

Ito, Suzuki, Asayama, Ito, & Endo, 2000). However, the neural mechanisms through which light modulates cognitive functions are not well understood.

For diurnal species, including humans, light promotes alertness, which is essential for optimal cognitive function (Brainard & Hanifin, 2005). Humans receiving bright light exposure during the day have lower sleepiness and fatigue scores compared to those in a dim light condition (Ruger, Gordijn, Beersma, de Vries, & Daan, 2006). Neuroimaging studies have shown that daytime bright light exposure instantly increases activity in the subcortical regions that support alertness/arousal even before affecting cortical areas involved in cognitive processes and performance (Vandewalle et al., 2006). Similar results are obtained when using blue-enriched light at a ~460 nm wavelength (Vandewalle et al., 2007a,b), which is the preferred wavelength for the retinal ganglion cells that are responsible for nonimage-forming photoreception (Do and Yau, 2010; Lucas et al., 2014).

Light also modulates human attention and executive functions involved in cognitive processing. Measuring brain activities using electroencephalogram (EEG), shows that daytime exposure to blue light increases the amount of attentional resource allocated to cognitive tasks (An, Huang, Shimomura, & Katsuura, 2009; Okamoto and Nakagawa, 2015). Furthermore, bright light therapy has been used in patients with attention-deficit/hyperactivity disorder, who show improvement in measures of both attention and executive function (Rybak, McNeely, Mackenzie, Jain, & Levitan et al., 2006).

In addition to the acute effects of bright-light exposure on arousal and attention, chronic changes in ambient lighting conditions can produce long-lasting effects on brain and behavior. For example, laboratory rats housed in constant light during early development are resistant to the disruptive effects of constant light on circadian rhythms throughout their adulthood, suggesting that alterations in ambient illumination can lead to long-term changes in the brain (Cambras et al., 1998). Mice housed under different photoperiods or day-length over early development also show enduring difference in their dorsal raphe serotonin neurons, including their electrical properties and neurotransmitter content (Green, Jackson, Iwamoto, Tackenberg, & McMahon, 2015). In postmortem human brain tissue, the number of midbrain dopaminergic neurons is higher in those who died in summer compared to those in winter (Aumann et al., 2016). Our own work using Nile grass rats (*Arvicanthis niloticus*), a diurnal rodent species, shows an increased number of dopaminergic and serotoninergic neurons in animals that had been housed over 4 weeks under daytime bright light (~1000 lux) as compared to those kept under daytime dim light (~50 lux) (Deats, Adidharma, & Yan, 2015; Leach, Adidharma, & Yan, 2013a). On the basis of these findings, we hypothesized that long-lasting changes in the brain, beyond temporary enhancement of arousal or attention, are likely to contribute to the superior cognitive performance associated with brighter illumination.

To test this hypothesis, the present study utilized the diurnal Nile grass rat and hippocampal-dependent spatial learning/memory as model systems to explore the neural mechanisms through which ambient lighting conditions impact cognitive functions. Spatial learning and memory was assessed using the Morris Water Maze (MWM) task,

which has been has been widely used in rodent species (Morris, 1981; Vorhees and Williams, 2006). Successful performance in MWM task has been shown to rely upon an intact hippocampus (Aggleton, Hunt, & Rawlins, 1986; Morris, Garrud, Rawlins, & O'keefe, 1982; Scoville and Milner, 2000) and is strongly correlated with hippocampal expression of brain-derived neurotrophic factor (BDNF) and dendritic plasticity (Conrad, McLaughlin, Huynh, El-Ashmawy, & Sparks, 2012; Kesslak, So, Choi, Cotman, & Gomez-Pinilla, 1998). Therefore, we focused our investigation on the hippocampus by examining its expression of BDNF and its dendritic spine morphology. The present study provides novel insights into the mechanisms responsible for the effects of ambient light on cognitive function, and has identified the grass rat as a useful diurnal animal model to further elucidate the underlying neural substrates for the behavioral effects of differential light exposure.

2 | EXPERIMENTAL PROCEDURES

2.1 | Subjects

Male unstriped Nile grass rats (*Arvicanthis niloticus*) from our breeding colony at Michigan State University were used for all experiments. All animals were entrained to a 12:12 h light-dark (LD, ~300 lux during the day) cycle and were given food (PMI Nutrition Prolab RMH 2000, Brentwood, MO) and water *ad libitum*. All grass rats were group-housed prior to the start of the behavioral testing and then single-housed for the duration of the study in Plexiglas cages (34 × 28 × 17 cm³), under either a 12:12 h bright light-dark (brLD, ~1,000 lux during the day) or dim light-dark (dimLD, ~50 Lux) cycle as described in our previous studies (Deats, Adidharma, Lonstein, & Yan, 2014; Leach et al., 2013a). A PVC tube was provided in the cage as a form of enrichment and as a hut for the animals. All experiments were performed in compliance with guidelines established by the Michigan State University Institutional Animal Care and Use Committee (IACUC), and the National Institutes of Health (NIH) guide for the Care and Use of Laboratory Animals.

2.2 | Morris water maze

Three cohorts of animals (n = 8/lighting condition) were used in this experiment. In the first cohorts, animals were housed in either brLD or dimLD for 1 week prior to being trained on the Morris Water Maze (MWM); while in the 2nd cohort, animals were housed in each condition for 4 weeks prior to MWM training. For the 3rd cohort, animals either remained in the colony condition (~300 lux) and then transferred to dimLD for 4 weeks prior to training on the MWM, or housed in dimLD for 4 weeks before being transferred to brLD for an additional 4 weeks prior to training. For all cohorts and conditions, during the last week before training, the animals were handled daily for 10 min to reduce novelty-induced stress that may stem from the experimenter's handling of the animals (Leger et al., 2013). Handling was performed in the animals' home cage in the behavioral testing room. Animals were trained and tested during *zeitgeber* time (ZT) 5–7, lights on was defined as ZT0; the light intensity in the testing room was

~300 lux. Training on the MWM was performed as previously described using a circular pool (60 cm depth × 122 cm diameter) with a platform (15 cm diameter) located 2 cm under the water level and ~30 cm away from the perimeter of the pool (Martin-Fairey and Nunez, 2014). The water was made opaque with nontoxic white tempera paint and kept at 26 ± 2°C; different geometrical cues were posted up on each wall of the room for spatial orientation. Prior to the hidden-platform training, animals underwent a one-day cued-platform training, during which the water was clear and the platform was kept above water. This was done to ensure that any deficits seen during the hidden platform training were not due to impaired motor functions (Vorhees and Williams, 2006). As a prerequisite, all animals included in the following experiments located the platform in less than 2 min when it was visible. For the hidden platform procedure, each animal completed two training trials per day over 5 days with each trial being a maximum of 2 min in length with an intertrial interval of 30 s. If the animal failed to locate the platform at the end of the 2 min period, it was guided towards the platform, and given a latency score of 120 s. On the sixth day, reference memory was tested 24 h after the last training session by removing the platform from the MWM and allowing each grass rat to swim for 1 min to measure the following parameters: time spent in the goal quadrant where the platform had been located, swim speed, and thigmotaxis, i.e., time spent swimming next to the wall (Morris, 1984). All behavior videos were loaded into Noldus *Ethovision* (*XT* 8.5, Noldus Information Technology, Netherlands) and scored by a experimenter who was blind to the experimental conditions.

2.3 | Immunohistochemistry (IHC)

Animals tested in the MWM were left undisturbed for two days before being used for the IHC analysis. Another group of animals that was housed under the same lighting conditions, i.e., 4 weeks of either brLD or dim LD, but without behavioral training/testing, was also used for the IHC analysis. All animals were transcardially perfused at ZT 5–7 with saline followed by 4% paraformaldehyde (PFA). Brains were postfixed and cryo-protected, then three alternate sets of 40 μm sections were collected using a cryostat. Ten sequential sections containing the dorsal HPC from one alternate set were processed for IHC using anti-BDNF primary antibody (1:5,000, raised in rabbit, ab101747, Abcam, Cambridge, UK). The specificity of the antibody in grass rats has been verified in a previous study (Martin-Fairey and Nunez, 2014). The IHC procedures were carried out as described in our previous studies using 3,3′-Diaminobenzidine (DAB) and 4% Nickel Sulfate for colorimetric reaction (Adidharma, Leach, & Yan, 2012; Deats et al., 2014; Leach et al., 2013a; Leach, Ramanathan, Langel, & Yan, 2013b). After the IHC reaction, sections were mounted, dehydrated/clarified and then coverslipped using Permount (Fisher Scientific, NH). Photomicrographs of the dorsal hippocampus were taken using a CCD camera attached to a Nikon light microscope and analyzed using Image J (NIH) as described in previous studies (Adidharma et al., 2012; Deats et al., 2014; Leach et al., 2013a,b). The number of BDNF-ir cells was determined for the CA1, CA3, and dentate gyrus (DG) subregions of the hippocampus with a 200 × 400 μm counting box (Figure 1, Supporting Information).

2.4 | Golgi staining

Behaviorally naïve animals were used in this study. Grass rats were housed in either brLD or dimLD (n = 7/condition) for 4 weeks prior to transcardial perfusion (at ZT 5–7) with a phosphate buffer followed with a Rapid-Golgi fixative solution [modified from (Patro, Kumar, & Patro, 2013)]. Brains were postfixed in the same solution for 24 h, then transferred to 3% potassium dichromate for three days before immersion in 1% AgNO$_3$ for eight days. Brains were placed in 20% sucrose for 48 h prior to sectioning at 100 μm using a cryostat. Sections were processed through an ethanol dehydration series and were clarified with xylene. Sections were mounted onto gelatin-coated slides and coverslipped with Permount (Fisher Scientific, NJ). For quantification, images of dendritic spines were captured using a CCD video camera (CX9000, MBF bioscience, VM, USA) attached to a light microscope using an oil immersion lens (Nikon Instruments, NY) and spines were quantified using ImageJ with the AnalyzeSkeleton plug-in (Ignacio Arganda-Carreras, http://fiji.sc/wiki/index.php/). CA1 apical dendritic spines were analyzed from 20μm segments of four distinct dendritic branches per neuron, a total of six neurons were analyzed per brain (Pyter, Reader, & Nelson, 2005).

2.4.1 | Spine morphology

Animals were housed in either brLD or dimLD for 4 weeks (n = 6/condition) without behavioral training or testing (behaviorally naïve). They then received bilateral injection into dorsal hippocampus of herpes simplex virus expressing green fluorescent protein (HSV-GFP, Massachusetts Institute of Technology Viral Core Facility) (Rodriguez, Ehlenberger, Dickstein, Hof, & Wearne, 2008). Needles of 26-gauge (Hamilton Company, Reno, NV) were placed bilaterally at the following coordinates from bregma: −0.1 mm A-P (anteroposterior); ± 2.0 mm L-M (mediolateral); −2.7 mm D-V (dorsoventral) from brain surface. Purified high-titer HSV-GFP (0.5 μL) was infused at a rate of 0.1 μL/min, after infusions the needle rested at the site for 5 min prior to extraction.

After 48 h postsurgery to allow for maximal GFP expression, animals were perfused transcardially with PBS followed by 4% paraformaldehyde. Sections were obtained at 100 μm thickness and mounted onto subbed glass slides with ProLong® Diamond Antifade Mountant (ThermoFisher Scientific, Waltham, MA). For detailed morphological analyses of dendritic spines, samples were imaged on a Nikon A1Rsi laser scanning confocal microscope utilizing a 100× Plan Apo TIRF DIC-oil immersion objective (total magnification of 1,000×). To visualize GFP, the samples were excited with a 488 nm laser and the fluorophore emission was captured by a 525/50 band-pass (BP) filter. A z-stack was obtained for each sample for dendritic spine analysis.

For each animal, five neurons (two dendritic segments/neuron) were analyzed. Z-stacks were were used to achieve three-dimensional reconstruction utilizing the NeuronStudio freeware morphometric program, which allows for accurate visualization and aids in reducing experimenter bias (Rodriguez et al., 2008). Dendritic spine density for the dendritic segments was quantified and grouped by subtypes (e.g., thin, stubby, and mushroom) based on neck length and head diameter. Thin and mushroom spine subtypes are classified as having visible necks with the major difference being that the head diameter of thin spines is not
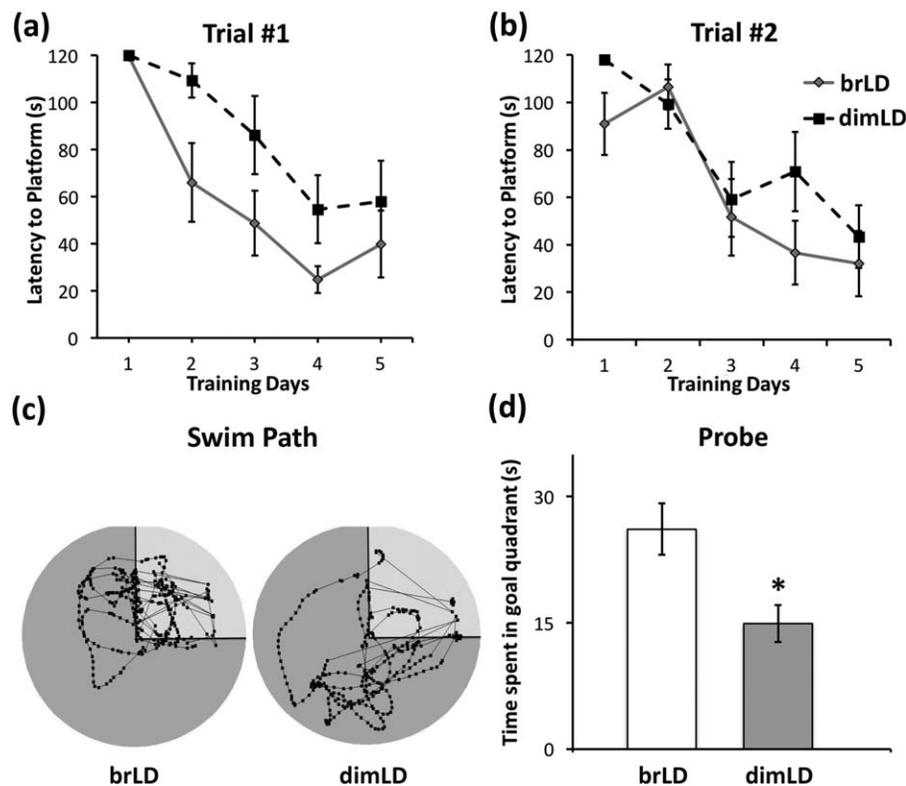
FIGURE 1 Impaired MWM performance of grass rats housed in dimLD as compared to those in brLD condition over 4 weeks. (a) Latency of animals to locate the platform during trial 1 (24 h delay) over the 5 training days. Grass rats housed in brLD were able to locate the platform significantly faster in the than those housed in dimLD (main effect of training days: $F(4,56) = 16.493$, $p < 0.001$; main effect of lighting condition: $F(1,14) = 4.652$, $p < 0.05$); interaction between training days and lighting condition ($F(4,56) = 0.953$, $p > 0.05$). (b) Latency of animals to locate the platform during trial 2 (30 s 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 amount of time searching for the platform in the goal quadrant in the probe test when compared to grass rats in the dimLD group. *, $p < 0.05$

notably different from the neck diameter, while mushroom spines' head diameters are clearly larger than their neck diameter. Stubby spines are characterized as having a large head diameter along with no neck presence (Bourne and Harris, 2008; Hering and Sheng, 2001).

2.5 | Data analysis

Statistical analysis was performed using SPSS (version 24, IBM, Armonk, North Castle, NY). For MWM behavioral data, the latency to reach the platform was analyzed using 2×5 Mixed ANOVAs with lighting condition as the between–subjects factor and training days as the repeated measures factor for trials 1 and 2 separately. In the case that there was a significant interaction, Holm-method comparisons were used to evaluate group differences across all five training days; when there was no interaction, only main effects were interpreted. Two-tailed independent samples student's t-tests were used to assess group differences on the amount of time spent in the goal quadrant, swim speed, and thigmotaxis (i.e., time spent swimming in the periphery not representative of a search pattern) during the probe tests. The number of BDNF-ir cells in each subregion (Figure 1, Supporting Information) and dendritic spine density in CA1 were compared between lighting conditions using two-tailed independent samples student's

t-tests. The threshold for statistical significance for all analyses was established at $p < 0.05$.

3 | RESULTS

3.1 | Chronic daylight deficiency impairs MWM performance

For the first trial of each day, both groups kept under either dim- or br-LD for 4 weeks showed significant improvement in their performance (i.e., latency to find the platform) over the 5 training days, but the performance of the brLD group was superior to that of the dimLD animals (Figure 1a; main effect of training days: $F(4,56) = 16.493$, $p < 0.001$; main effect of lighting condition: $F(1,14) = 4.652$, $p < 0.05$). There was no significant interaction between training days and lighting condition ($F(4,56) = 0.953$, $p > 0.05$). That group difference was absent for trial 2 ($F(1,14) = 1.377$, $p > 0.05$), which was conducted 30 s after trial 1 (Figure 1b). By the last two training days, the majority of the animals successfully located the platform during training trails (Figure 2, Supporting Information). During the probe trial when the platform was removed, the brLD animals concentrated the search within the goal quadrant, in contrast to the dimLD animals (Figure 1c). Comparison of the time spent
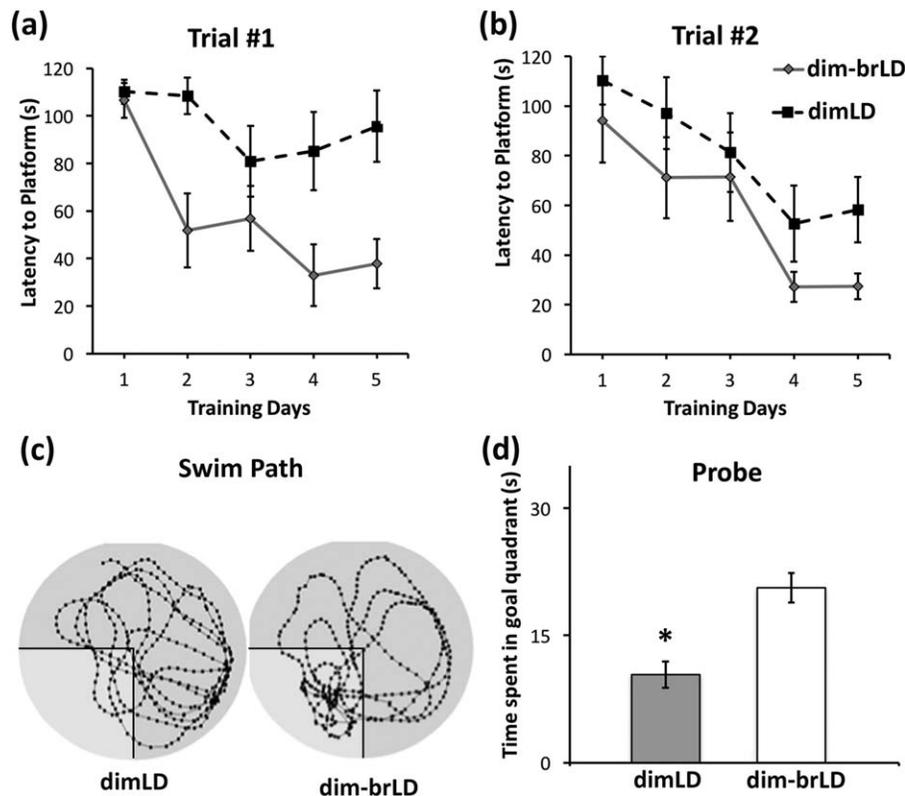
FIGURE 2 Subsequent brLD housing (dim-brLD) restored the impaired MWM performance of animals housed in dimLD conditions for 4 weeks. (a) Latency of animals to locate the platform during the first trial (main effect of training days: ($F(4,56) = 15.05$, $p < 0.001$); main effect of housing condition: ($F(1,14) = 12.942$, $p = 0.003$); interaction between training days and housing condition: $F(4,56) = 2.38$, $p = 0.062$). (b) Latency of animals to locate the platform during the 2nd trial, 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). Time spent searching for the platform in the goal quadrant in the probe test. *, $p < 0.05$

on the goal quadrant by each group showed a significant difference with the brLD spending more time on the quadrant than the dimLD group (Figure 1d; $t(14) = 2.98$, $p = 0.01$). The performance of the dimLD group was not significantly different from chance (15 s; $t(7) = -0.057$, $p = 0.956$). The groups did not differ significantly with respect to swim speed ($t(14) = 0.002$, $p > 0.05$) and thigmotaxic behavior ($t(14) = -0.76$, $p > 0.05$). In contrast to the animals housed in each condition for 4 weeks, identical testing of animals kept in brLD or dimLD for just one week did not result in group differences on any of the dependent variables (Figure 3, Supporting Information).

3.2 | Impaired MWM performance resulting from daytime light deficiency can be restored by transferring to brLD condition

To determine if the impairments in spatial learning/memory due to light restriction are reversible, the animals initially housed for 4 weeks in dimLD were transferred to brLD and kept there for 4 weeks before testing. The transferred animals showed superior performance as compared to those kept in dimLD. For trial 1 there was a significant main effect of training days ($F(4,56) = 15.05$, $p < 0.001$) and housing condition on the latency to reach the platform ($F(1,14) = 12.942$, $p = 0.003$), with no significant interaction (Figure 2a; $F(4,56) = 2.38$, $p = 0.062$). Individual

group comparisons showed superior performance for the animals in the reversal condition (i.e., dimLD-brLD) over those in the dimLD group for days 2, 4, and 5 of training. No group differences were detected for the latency data for trial 2 (Figure 2b). During the probe trial, animals transferred from dimLD to brLD concentrated the search for the platform within the goal quadrant in contrast to the dimLD animals (Figure 2c). The transferred animals also spent more time in the goal quadrant than the dimLD group (Figure 2d, $t(14) = 4.387$, $p = 0.001$). There were no significant differences in swim speed ($t(14) = 0.488$, $p > 0.05$) or thigmotaxis ($t(14) = 0.116$, $p > 0.05$) between groups.

3.3 | Ambient lighting condition modulates hippocampal BDNF expression

BDNF-ir in the hippocampus was reduced in the dimLD group when compared to the brLD group (Figure 3a). The average number of BDNF-ir cells was analyzed in CA1, CA3, and DG. The number of BDNF-ir cells were consistently lower across the three areas for the dimLD group, although statistical significance was reached only for CA1 ($t(10) = 3.05$, $p = 0.012$, Figure 3b). The data reported here are from animals that had been through MWM training. A separate cohort of animals without any behavioral testing was also compared for BDNF-ir (Figure 4, Supporting Information). Similar results were obtained, with lower number of
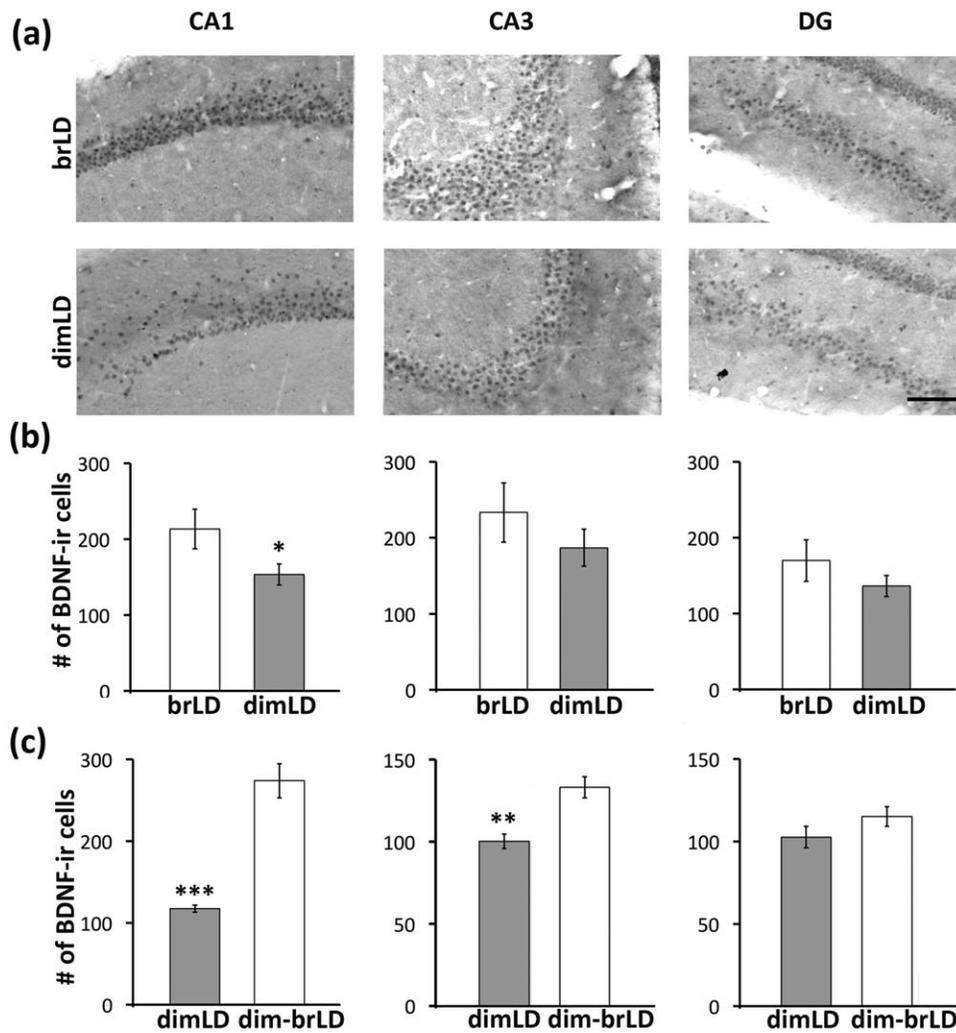
FIGURE 3 Ambient light condition modulates hippocampal BDNF expression. (a) Representative photomicrographs of BDNF immunochemical staining within the CA1, CA3, and DG of the hippocampus of grass rats housed in brLD or dimLD condition. (b) Number of BDNF-labeled cell bodies in each subregion of the hippocampus in animals housed in brLD or dimLD condition. (c). Number of BDNF-labeled cell bodies in each subregion of the hippocampus in animals housed in dimLD and those initially housed in dimLD then switched to brLD. Scale bar, 100 μm. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

BDNF-ir cells in the CA1 of dimLD as compared to brLD condition in these naïve animals ($t(10) = 6.798$, $p < 0.001$). Similar to the behavioral reversal in MWM performance seen when the dimLD animals were transferred to brLD for 4 weeks, there was an increase in hippocampal BDNF-ir in the transferred animals as compared to those kept in dimLD (Figure 3c). A significant increase was observed in both CA1 ($t(10) = 7.307$, $p < 0.001$) and CA3($t(10) = 4.183$, $p = 0.002$).

3.4 | Ambient light modulates CA1 apical dendritic morphology

In addition to BDNF expression, ambient light also modulates structural plasticity in the hippocampus. The morphology of golgi-stained apical dendrites was analyzed in CA1 of animals from different lighting condition (Figure 4). When the brLD and dimLD groups were compared (Figure 4a,b), there was a significant reduction of apical dendritic spine density in the dimLD ($t(8) = 5.103$, $p = 0.001$). Following transferring to

the brLD condition (Figure 4c,d), the dimLD-brLD group showed a significant increase in apical dendritic spine density as compared to those kept in dimLD ($t(10) = 10.062$, $p < 0.001$).

The morphology of apical dendritic spines was further analyzed using HSV-GFP expression in hippocampal neurons (Figure 5). Examples of labelled apical dendrites from animals kept four weeks in brLD or dimLD are shown in Figure 5a. Group comparisons of the abundance of different types of spines in CA1 found significant higher density of mushroom ($t(9) = 2.680$, $p < 0.05$) and stubby spines ($t(9) = 4.605$, $p = 0.001$) in the BLD group compared to the DLD animals, with no significant group differences for density of thin spines (Figure 5b).

4 | DISCUSSION

We show here that in diurnal Nile grass rats, chronic conditions of ambient lighting can influence cognition in a way similar to that observed in humans, such that bright light is beneficial over dim light
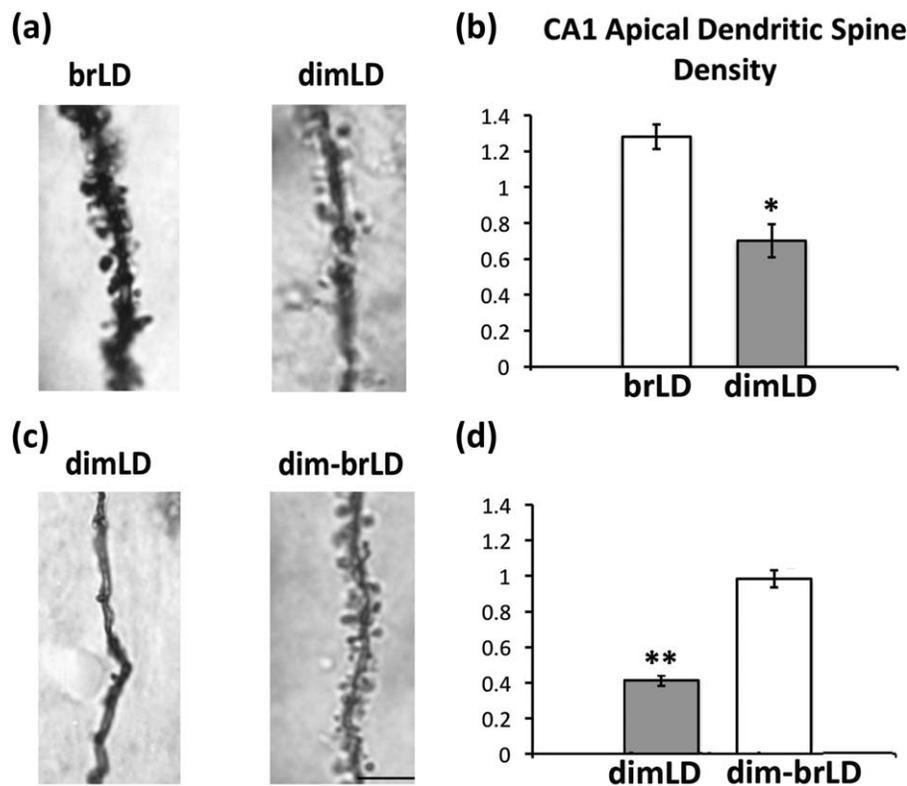
FIGURE 4 Golgi staining of CA1 apical dendrites. (a) Representative photomicrograph and (b) quantification of dendritic spines of grass rats housed in either brLD or dimLD condition for 4 weeks. (c) Representative photomicrograph and (d) quantification of dendritic spines of grass rats housed in dimLD or initially in dimLD then transferred to brLD. Scale bar, 5 μm. *, $p < 0.01$; **, $p < 0.001$

for cognitive performance. In addition, we found that lighting condition can modulate the level of hippocampal BDNF expression as well as structural plasticity within the hippocampus.

The Nile grass rat is a well-established diurnal rodent model that has been used in various research areas including circadian rhythms and sleep/arousal systems to show how the control of those functions differs from that of nocturnal rodents (Castillo-Ruiz, Nixon, Smale, & Nunez, 2010; Gall, Smale, Yan, & Nunez, 2013; Gall, Yan, Smale, & Nunez, 2014; Nixon and Smale, 2007; Novak, Harris, Smale, & Nunez, 2000; Ramanathan, Nunez, & Smale, 2008; Schwartz and Smale, 2005). Because of the different, and often opposite, effects of light on diurnal and nocturnal species (e.g., light promotes wakefulness/arousal in diurnal animals including humans, but induces sleep in nocturnal ones), a diurnal model is of crucial importance for a mechanistic understanding how light modulates cognition in humans (Challet, 2007; Smale, Lee, Nunez, 2003). Diurnal rodent models i.e., Mongolian gerbils, fat sand rats and Nile grass rats have been used for investigating the impact of lighting condition on brain and behavior in various lighting paradigms including total darkness, short-photoperiod or dim light exposure at night (Ashkenazy-Frolinger, Kronfeld-Schor, Juetten, & Einat, 2010; Einat, Kronfeld-Schor, & Eilam, 2006; Lau et al., 2011) (Fonken, Kitsmiller, Smale, & Nelson, 2012). The lighting paradigm used in the present study was designed to manipulate daytime light intensity while keeping the day-length or photoperiods constant. By having photoperiods remain constant, our findings aim to be more ecologically relevant to

humans because, unlike animals in nature under sunlight, much of our living environment is comprised of artificial light. Therefore, we do not experience drastic changes in day-length, but rather variations in the quality of light i.e., spectrum or intensity (Hubert, Dumont, & Paquet, 1998).

After being kept in dim light during the day (dimLD) for 4 weeks, grass rats showed a deficit in the MWM task compared to the performance of animals kept under brLD for the same duration. The deficit was evident for both the first trial of each training day and for the probe test, in which the amount of time the dimLD animals spent in the goal quadrant was at chance level (Figure 1). There were no group differences for animals kept in the two lighting conditions for just one week, thus suggesting that the detrimental effects of dim light develop over time (Figure 3, Supporting Information). Further, since both groups were tested under identical intermediate lighting conditions, the superior performance of the animals in brLD for 4 weeks is not due to the acute effects of bright light on performance, as has been reported in human studies (Knez, 1995; Riemersma-van der Lek et al., 2008; Royer et al., 2012; Yamadera et al., 2000). Swimming speed did not differ across groups; therefore, group differences are not likely to reflect deficits in motivation (Lubbers, van den Bos, & Spruijt, 2007) or sensory-motor functions (Vorhees and Williams, 2006). Even though, dimLD housing has been shown to be anxiogenic for grass rats in the open field test (Ikeno, Deats, Soler, Lonstein, & Yan et al., 2016), the lack of group differences in the display of thigmotaxis in the MWM suggests
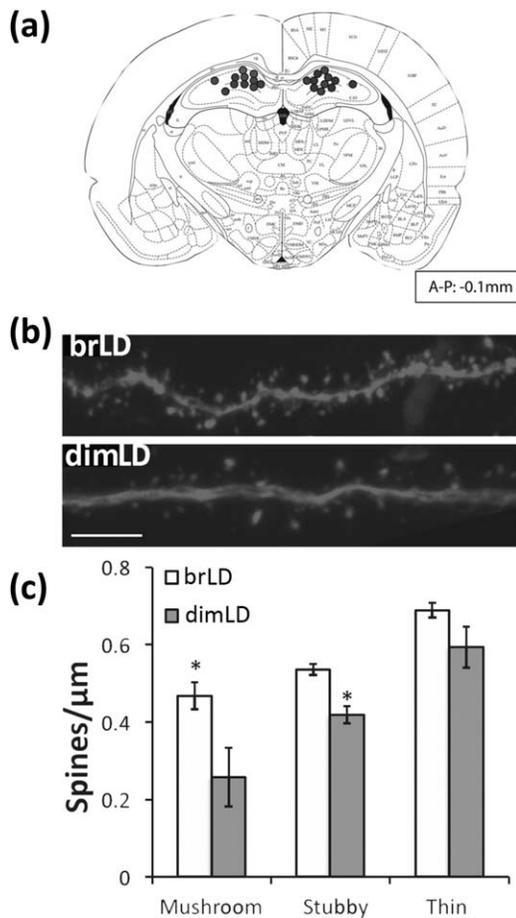
(a)

A-P: -0.1mm

(b)

brLD

dimLD

(c)

FIGURE 5 Hippocampal apical dendrites visualized by HSV-GFP expression. (a) The injection sites of the HSV-GFP. (b) Representative photomicrophs of HSV-GFP expression. (c) Quantification of the density of dendritic spine sub-types. Scale bar, 5 μm. *, $p < 0.01$;

hippocampal-dependent reference memory is necessary for remembering the location of the platform from one training day to the next. Thus, the normal performance of dimLD animals on trial 2 may reflect an intact working memory and lack of dysfunction in the prefrontal cortex. Alternatively, the experience of trial 1 each day may reactivate a relatively weak reference memory (de Hoz, Martin, & Morris, 2004), which then supports the normal performance of the dimLD animals on trial 2. Regardless of the possible explanations for the improved performance of the dimLD animals on trial 2, our results point to an inability to consolidate a robust hippocampal-dependent memory over a 24 h interval. The results collectively suggest that long-term (4 weeks) light deficiency impairs consolidation of spatial memories, which is indicated by the rapid forgetting over a 24 h interval displayed by the dimLD animals. This rapid forgetting of reference memory in the MWM has been seen in studies with other animal models of hippocampal deficits e.g., epilepsy (Barkas et al., 2012), and hippocampal insulin resistance (Grillo et al., 2015).

MWM performance has been linked to hippocampal expression of BDNF (Kesslak et al., 1998), a member of the neurotrophin family of growth factors, which has been shown to be involved in learning and is crucial for long-term memory (Bekinschtein et al., 2007, 2008; Lu, Christian, & Lu, 2008). Analyses of hippocampal BDNF expression and apical dendritic spines revealed a significant effect of ambient light on the structural plasticity of the hippocampus. Following 4 weeks of dimLD housing, there was a significant reduction in the number of BDNF-ir cells in the CA1 sub-region, compared to the animals in brLD and to those initially housed in dimLD then switched to brLD for another 4 weeks (Figure 3). It is noteworthy that the brain samples from the two cohorts of animals i.e., 4 weeks in brLD versus dimLD (Figure 3b) and 4 weeks in colony lighting (~300 lux) followed by 4 weeks dimLD versus 4 weeks dimLD followed by 4 weeks brLD (dim-brLD, Figure 3c) were processed for ICC separately, therefore, the results cannot be directly compared. Nonetheless, the differences between the dimLD and dim-brLD in the last cohort (Figure 3c) appear to be greater than that in Figure 3b when dimLD and brLD were compared. The greater differences in the last cohort (Figure 3c) may due to the interaction between the lighting condition and prolonged (8 weeks) singly housing of the animals. Since these animals had been through MWM training/testing, the differences observed in BDNF-ir could have resulted from their housing condition, or alternatively, from their experience with the MWM, or the interaction of the two factors. Thus, we repeated the analysis in naïve animals. The results revealed a similar pattern with higher BDNF-ir in brLD as seen in the animals exposed to MWM training, thus suggesting that the difference in BDNF-ir was indeed due to the effects of the lighting condition and not the result of differential performance of the two groups on the MWM (Figure 4, Supporting Information).

BDNF signaling modulates dendritic spine growth in the CA1 (Tyler and Pozzo-Miller, 2003). The growth of dendritic spines in the hippocampus, particularly within the CA1 region, has been linked to the formation of new synapses and improved learning and memory (Matsuzaki, Honkura, Ellis-Davies, & Kasai, 2004; Moser, Trommald, & Andersen, 1994; Tsien, Huerta, & Tonegawa, 1996). We found reduced

that the memory deficit of the dimLD animals is unlikely the result of enhanced anxiety during training/testing. When the dimLD grass rats were rehoused under the brLD condition for another 4 weeks, the animals performed significantly better than those in dimLD, suggesting that subsequent exposure to bright light can restore impaired spatial memory due to previous light restriction (Figure 2).

Interestingly, the effect of long-term light restriction on latency to find the platform during training, was only significant for trial 1 of each day (Figures 1a and 2b), suggesting that the retention of the memory for the platform location was impaired in the dimLD animals after a 24 h interval but not for the 30 s between-trial interval; a similar conclusion is supported by the results of the probe trial, which occurs a day after the last training trial. However, the effect of lighting condition on latency to find the platform was not significant for trial 2 of each day (Figure 1b and 2b), indicating that exposure to the water maze on trial 1 of each day was sufficient to bring the performance of the dimLD animals to the level of the brLD group in the second trial 30 s later. In the MWM, working memory, which involves the prefrontal cortex (Jones, 2002), is engaged as the animal searches for the escape platform on subsequent trials of the same training day, whereas

CA1 apical dendritic spine density in dimLD animals compared to brLD and dimLD-to-brLD groups (Figure 4), suggesting a possible change in CA3-CA1 connectivity, a crucial circuit for spatial memory (Kodama, Usui, Honda, & Kimura, 2005; Marston et al., 2008). Following 4 weeks of rehousing the dimLD group in the brLD condition, we found a significant increase in both BDNF-ir and dendritic spine density in the hippocampus. These findings indicate restored hippocampal function underlies the improvement of MWM performance of animals under the same lighting regimen (Figure 2). It should be noted that the animals in the present study were all young adults (4–6 months old). Whether this level of plasticity is retained in older animals and how aging may impact the modulatory effects of light on hippocampal function requires further investigation.

It has been proposed that most excitatory synapses are located at dendritic spines (Harris, 1999; Matus, 2000), and their retraction or generation may underlie the neural mechanisms for learning and memory (Segal, 2017). A more detailed morphometric analysis on CA1 apical dendritic segments revealed a significant reduction of stubby and mushroom spines in dimLD compared to the brLD group (Figure 5). Various studies demonstrate that after tetanic stimulation or behavioral training engaging the hippocampus, the spine apparatus prevalent in mushroom spines (Spacek and Harris, 1997) recruits a wide array of molecules that enhance synaptic plasticity (Engert and Bonhoeffer, 1999; Matsuo, Reijmers, & Mayford, 2008; Ostroff, Fiala, Allwardt, & Harris, 2002). Therefore, the observed lower number of CA1 mushroom spines may reflect a degradation of synaptic plasticity that is correlated with impaired performance in the MWM. The changes in BDNF expression, dendritic spine density, as well as spine morphology within the CA1, collectively suggest that ambient light modulates structural plasticity in the hippocampus.

The functional and structural changes in the hippocampus support the hypothesis that long-lasting changes in the brain, beyond temporary enhancement of arousal or attention, contribute to the superior cognitive performance associated with brighter illumination. Consistent with this hypothesis, seasonal variation has been reported in human cognitive brain responses, measured by P300 event-related brain potentials (Kosmidis, Duncan, & Mirsky, 1998; Polich and Geisler, 1991) and fMRI (Meyer et al., 2016). And the P300 amplitude has been shown to be influenced by seasonal variation in the available amount of sunshine (Polich and Geisler, 1991). Enhanced cognitive function by light has traditionally been explained in reference to sleep and circadian rhythms (Chellappa et al., 2011), and sleep and circadian regulation certainly play a role in memory and hippocampal functions (Smarr, Jennings, Driscoll, & Kriegsfeld, 2014; Walker and Stickgold, 2006). However, lighting conditions can also influence learning/memory through circadian-independent mechanisms likely to involve melanopsin-based photoreception (LeGates et al., 2014). Our results provide evidence that lighting condition modulates the functional connectivity of the neural circuit within the hippocampus. More work is required to further elucidate the neural pathways mediating the effects of ambient light on the hippocampus. A possible candidate would be the hypothalamic orexin/hypocretin neurons, which have been implicated in many important functions including wakefulness, energy

homeostasis, emotion, and cognition (Gerashchenko and Shiromani, 2004; Tsujino and Sakurai, 2009). Our previous work in grass rats has shown that the number of orexin-ir neurons and the density of orexin-ir fibers are affected by lighting conditions, with higher levels of orexin-ir in brLD than in dimLD groups (Deats et al., 2014); and orexin pathways mediate the effects of light on other brain regions, i.e., the dorsal raphe (Adidharma et al., 2012) and hypothalamic dopaminergic neurons (Deats et al., 2015). Orexinergic cells project directly to the hippocampus in both nocturnal laboratory rats and diurnal grass rats (Nixon and Smale, 2007; Peyron et al., 1998). Thus, the orexin system is well positioned to mediate the effects of light on hippocampal-dependent learning and memory, an idea that will be further explored in future studies.

The present study is a first step towards a better understanding of how ambient light modulates cognitive functions in diurnal species. Such knowledge is significant for the design of lighting environments that promote optimal cognitive function. In the United States, a majority of the population spends ∼90% of their time indoors, where the lighting is less bright than outdoors (Klepeis et al., 2001). Even in optimal environments, light deficiency can occur as a result of reduced ocular transmission related to retinal disease or aging (Chen et al., 2013; Coleman, Chan, Ferris, & Chew, 2008; de Zavalia et al., 2011; Fernandez et al., 2013; Higuchi et al., 2013). Although light pollution or light exposure at night has recently been recognized as a negative factor for ecology and human health (Chepesiuk, 2009; Falchi, Cinzano, Elvidge, Keith, & Haim, 2011), the consequence of insufficient light during the day has received less attention. Our finding that 4 weeks of daytime light deficiency leads to a reduction in the functional connectivity within the hippocampus and to impairments in spatial learning and memory underscore the salient effects of light on our brain and behavior. A mechanistic understanding of the effects of light on cognition can help to identify risk factors for cognitive decline and contribute to the development of more effective prevention and treatment of cognitive impairment in clinical populations.

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REFERENCES

Adidharma, W., Leach, G., & Yan, L. (2012). Orexinergic signaling mediates light-induced neuronal activation in the dorsal raphe nucleus. *Neuroscience*, *220*, 201–207.

Aggleton, J. P., Hunt, P. R., & Rawlins, J. N. (1986). The effects of hippocampal lesions upon spatial and non-spatial tests of working memory. *Behavioural Brain Research*, 19(2), 133–146.

An, M., Huang, J., Shimomura, Y., & Katsuura, T. (2009). Time-of-day-dependent effects of monochromatic light exposure on human cognitive function. *Journal of Physiological Anthropology*, 28(5), 217–223.

Ashkenazy-Frolinger, T., Kronfeld-Schor, N., Juetten, J., & Einat, H. (2010). It is darkness and not light: Depression-like behaviors of diurnal unstriped Nile grass rats maintained under a short photoperiod schedule. *Journal of Neuroscience Methods*, 186(2), 165–170.

Aumann, T. D., Raabus, M., Tomas, D., Prijanto, A., Churilov, L., Spitzer, N. C., & Horne, M. K. (2016). Differences in number of midbrain dopamine neurons associated with summer and winter photoperiods in humans. *PLoS One*, 11(7), e0158847.

Barkas, L., Redhead, E., Taylor, M., Shtaya, A., Hamilton, D. A., & Gray, W. P. (2012). Fluoxetine restores spatial learning but not accelerated forgetting in mesial temporal lobe epilepsy. *Brain*, 135(Pt 8), 2358–2374.

Barkmann, C., Wessolowski, N., & Schulte-Markwort, M. (2012). Applicability and efficacy of variable light in schools. *Physiology & Behavior*, 105(3), 621–627.

Baron, R., Rea, M., & Daniels, S. (1992). Effects of indoor lighting (illuminance and spectral distribution) on the performance of cognitive tasks and interpersonal behaviors: The potential mediating role of positive affect. *Motivation and Emotion*, 16(1), 1–33.

Bekinschtein, P., Cammarota, M., Igaz, L. M., Bevilaqua, L. R., Izquierdo, I., & Medina, J. H. (2007). Persistence of long-term memory storage requires a late protein synthesis- and BDNF- dependent phase in the hippocampus. *Neuron*, 53(2), 261–277.

Bekinschtein, P., Cammarota, M., Katche, C., Slipczuk, L., Rossato, J. I., Goldin, A., . . . Medina, J. H. (2008). BDNF is essential to promote persistence of long-term memory storage. *Proceedings of the National Academy of Science United Science of America*, 105(7), 2711–2716.

Bourne, J. N., & Harris, K. M. (2008). Balancing structure and function at hippocampal dendritic spines. *Annual Review of Neuroscience*, 31, 47–67.

Brainard, G. C., & Hanifin, J. P. (2005). Photons, clocks, and consciousness. *Journal of Biological Rhythms*, 20(4), 314–325.

Cambras, T., Vilaplana, J., Torres, A., Canal, M. M., Casamitjana, N., Campuzano, A., & Diez-Noguera, A. (1998). Constant bright light (LL) during lactation in rats prevents arrhythmicity due to LL. *Physiology & Behavior*, 63(5), 875–882.

Castillo-Ruiz, A., Nixon, J. P., Smale, L., & Nunez, A. A. (2010). Neural activation in arousal and reward areas of the brain in day-active and night-active grass rats. *Neuroscience*, 165(2), 337–349.

Challet, E. (2007). Minireview: Entrainment of the suprachiasmatic clockwork in diurnal and nocturnal mammals. *Endocrinology*, 148(12), 5648–5655.

Chellappa, S. L., Gordijn, M. C., & Cajochen, C. (2011). Can light make us bright? Effects of light on cognition and sleep. *Progress in Brain Research*, 190, 119–133.

Chen, M., Hombrebueno, J. R., Luo, C., Penalva, R., Zhao, J., Colhoun, L., . . . Xu, H. (2013). Age- and light-dependent development of localised retinal atrophy in CCL2(-/-)CX3CR1(GFP/GFP) mice. *PLoS One*, 8(4), e61381.

Chepesiuk, R. (2009). Missing the dark: Health effects of light pollution. *Environmental Health Perspectives*, 117(1), A20–A27.

Coleman, H. R., Chan, C. C., Ferris, F. L., 3rd., & Chew, E. Y. (2008). Age-related macular degeneration. *Lancet*, 372(9652), 1835–1845.

Conrad, C. D., McLaughlin, K. J., Huynh, T. N., El-Ashmawy, M., & Sparks, M. (2012). Chronic stress and a cyclic regimen of estradiol administration separately facilitate spatial memory: relationship with hippocampal CA1 spine density and dendritic complexity. *Behavioral Neuroscience*, 126(1), 142–156.

de Hoz, L., Martin, S. J., & Morris, R. G. (2004). Forgetting, reminding, and remembering: The retrieval of lost spatial memory. *PLoS Biology*, 2(8), E225.

de Zavalia, N., Plano, S. A., Fernandez, D. C., Lanzani, M. F., Salido, E., Belforte, N., . . . Rosenstein, R. E. (2011). Effect of experimental glaucoma on the non-image forming visual system. *Journal of Neurochemistry*, 117(5), 904–914.

Deats, S. P., Adidharma, W., Lonstein, J. S., & Yan, L. (2014). Attenuated orexinergic signaling underlies depression-like responses induced by daytime light deficiency. *Neuroscience*, 272, 252–260.

Deats, S. P., Adidharma, W., & Yan, L. (2015). Hypothalamic dopaminergic neurons in an animal model of seasonal affective disorder. *Neuroscience Letter*, 602, 17–21.

Do, M. T., & Yau, K. W. (2010). Intrinsically photosensitive retinal ganglion cells. *Physiological Reviews*, 90(4), 1547–1581.

Einat, H., Kronfeld-Schor, N., & Eilam, D. (2006). Sand rats see the light: Short photoperiod induces a depression-like response in a diurnal rodent. *Behavioural Brain Research*, 173(1), 153–157.

Engert, F., & Bonhoeffer, T. (1999). Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature*, 399(6731), 66–70.

Falchi, F., Cinzano, P., Elvidge, C. D., Keith, D. M., & Haim, A. (2011). Limiting the impact of light pollution on human health, environment and stellar visibility. *Journal of Environmental Management*, 92(10), 2714–2722.

Fernandez, D. C., Sande, P. H., de Zavalia, N., Belforte, N., Dorfman, D., Casiraghi, L. P., . . . Rosenstein, R. E. (2013). Effect of experimental diabetic retinopathy on the non-image-forming visual system. *Chronobiology International*, 30(4), 583–597.

Fonken, L. K., Kitsmiller, E., Smale, L., & Nelson, R. J. (2012). Dim nighttime light impairs cognition and provokes depressive-like responses in a diurnal rodent. *Journal of Biological Rhythms*, 27(4), 319–327.

Forbes, D., Culum, I., Lischka, A. R., Morgan, D. G., Peacock, S., Forbes, J., & Forbes, S. (2009). Light therapy for managing cognitive, sleep, functional, behavioural, or psychiatric disturbances in dementia. *The Cochrane Database of Systematic Reviews*, (4), CD003946.

Gall, A. J., Smale, L., Yan, L., & Nunez, A. A. (2013). Lesions of the intergeniculate leaflet lead to a reorganization in circadian regulation and a reversal in masking responses to photic stimuli in the Nile grass rat. *PLoS One*, 8(6), e67387.

Gall, A. J., Yan, L., Smale, L., & Nunez, A. A. (2014). Intergeniculate leaflet lesions result in differential activation of brain regions following the presentation of photic stimuli in Nile grass rats. *Neuroscience Letter*, 579, 101–105.

Gerashchenko, D., & Shiromani, P. J. (2004). Different neuronal phenotypes in the lateral hypothalamus and their role in sleep and wakefulness. *Molecular Neurobiology*, 29(1), 41–59.

Green, N. H., Jackson, C. R., Iwamoto, H., Tackenberg, M. C., & McMahon, D. G. (2015). Photoperiod programs dorsal raphe serotonergic neurons and affective behaviors. *Current Biology*, 25(10), 1389–1394.

Grillo, C. A., Piroli, G. G., Lawrence, R. C., Wrighten, S. A., Green, A. J., Wilson, S. P., . . . Regan, L. P. (2015). Hippocampal insulin resistance impairs spatial learning and synaptic plasticity. *Diabetes*, 64(11), 3927–3936.

Harris, K. M. (1999). Structure, development, and plasticity of dendritic spines. *Current Opinion in Neurobiology*, 9(3), 343–348.

Hering, H., & Sheng, M. (2001). Dendritic spines: Structure, dynamics and regulation. *Nature Reviews Neuroscience*, 2(12), 880–888.

Heschong, L. (2002). Daylighting makes a difference. *Educational Facility Planner*, 37, 5–14.

Heschong, L., Wright, R., Okura, S., Klein, P., Simner, M., Berman, S., & Clear, R. (2002). Daylighting impacts on human performance in school. *Journal of Illuminating Engineering Society*, 31, 101–114.

Higuchi, S., Hida, A., Tsujimura, S., Mishima, K., Yasukouchi, A., Lee, S. I., ... Miyahira, M. (2013). Melanopsin gene polymorphism I394T is associated with pupillary light responses in a dose-dependent manner. *PLoS One*, 8(3), e60310.

Hubert, M., Dumont, M., & Paquet, J. (1998). Seasonal and diurnal patterns of human illumination under natural conditions. *Chronobiology International*, 15(1), 59–70.

Ikeno, T., Deats, S. P., Soler, J., Lonstein, J. S., & Yan, L. (2016). Decreased daytime illumination leads to anxiety-like behaviors and HPA axis dysregulation in the diurnal grass rat (Arvicanthis niloticus). *Behavioural Brain Research*, 300, 77–84.

Jones, M. W. (2002). A comparative review of rodent prefrontal cortex and working memory. *Current Molecular Medicine*, 2(7), 639–647.

Kesslak, J. P., So, V., Choi, J., Cotman, C. W., & Gomez-Pinilla, F. (1998). Learning upregulates brain-derived neurotrophic factor messenger ribonucleic acid: a mechanism to facilitate encoding and circuit maintenance? *Behavioural Neuroscience*, 112(4), 1012–1019.

Klepeis, N. E., Nelson, W. C., Ott, W. R., Robinson, J. P., Tsang, A. M., Switzer, P., ... Engelmann, W. H. (2001). The National Human Activity Pattern Survey (NHAPS): A resource for assessing exposure to environmental pollutants. *Journal of Exposure Analysis and Environmental Epidemiology*, 11(3), 231–252.

Knez, I. (1995). Effects of indoor lighting on mood and cognition. *Journal of Environmental Psychology*, 15(1), 39–51.

Kodama, T., Usui, S., Honda, Y., & Kimura, M. (2005). High Fos expression during the active phase in orexin neurons of a diurnal rodent, Tamias sibiricus barberi. *Peptides*, 26(4), 631–638.

Kosmidis, M. H., Duncan, C. C., & Mirsky, A. F. (1998). Sex differences in seasonal variations in P300. *Biological Psychology*, 49(3), 249–268.

Lau, B. W., Ren, C., Yang, J., Yan, S. W., Chang, R. C., Pu, M., & So, K. F. (2011). Light deprivation induces depression-like behavior and suppresses neurogenesis in diurnal mongolian gerbil (*Meriones unguiculatus*). *Cell Transplant*, 20(6), 871–881.

Leach, G., Adidharma, W., & Yan, L. (2013a). Depression-like responses induced by daytime light deficiency in the diurnal grass rat (*Arvicanthis niloticus*). *PLoS One*, 8(2), e57115.

Leach, G., Ramanathan, C., Langel, J., & Yan, L. (2013b). Responses of brain and behavior to changing day-length in the diurnal grass rat (*Arvicanthis niloticus*). *Neuroscience*, 234, 31–39.

LeGates, T. A., Fernandez, D. C., & Hattar, S. (2014). Light as a central modulator of circadian rhythms, sleep and affect. *Nature Reviews Neuroscience*, 15(7), 443–454.

Leger, M., Quiedeville, A., Bouet, V., Haelewyn, B., Boulouard, M., Schumann-Bard, P., & Freret, T. (2013). Object recognition test in mice. *Nature Protocols*, 8(12), 2531–2537.

Lu, Y., Christian, K., & Lu, B. (2008). BDNF: A key regulator for protein synthesis-dependent LTP and long-term memory? *Neurobiology of Learning and Memory*, 89(3), 312–323.

Lubbers, M. E., van den Bos, R., & Spruijt, B. M. (2007). Mu opioid receptor knockout mice in the Morris Water Maze: A learning or motivation deficit? *Behavioural Brain Research*, 180(1), 107–111.

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

Marston, O. J., Williams, R. H., Canal, M. M., Samuels, R. E., Upton, N., & Piggins, H. D. (2008). Circadian and dark-pulse activation of orexin/ hypocretin neurons. *Molecular Brain*, 1, 19.

Martin-Fairey, C. A., & Nunez, A. A. (2014). Circadian modulation of memory and plasticity gene products in a diurnal species. *Brain Research*, 1581, 30–39.

Matsuo, N., Reijmers, L., & Mayford, M. (2008). Spine-type-specific recruitment of newly synthesized AMPA receptors with learning. *Science*, 319(5866), 1104–1107.

Matsuzaki, M., Honkura, N., Ellis-Davies, G. C., & Kasai, H. (2004). Structural basis of long-term potentiation in single dendritic spines. *Nature*, 429(6993), 761–766.

Matus, A. (2000). Actin-based plasticity in dendritic spines. *Science*, 290 (5492), 754–758.

Meyer, C., Muto, V., Jaspar, M., Kusse, C., Lambot, E., Chellappa, S. L., ... Vandewalle, G. (2016). Seasonality in human cognitive brain responses. *Proceedings of the National Academy of Science of the United States of America*, 113(11), 3066–3071.

Mills, P., Tomkins, S., & Schlangen, L. (2007). The effect of high correlated colour temperature office lighting on employee wellbeing and work performance. *Journal of Circadian Rhythms*, 5(2), 2–10.

Morris, R. (1984). Developments of a water-maze procedure for studying spatial learning in the rat. *Journal of Neuroscience Methods*, 11(1), 47–60.

Morris, R. G., Garrud, P., Rawlins, J. N., & O'keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, 297(5868), 681–683.

Morris, R. G. M. (1981). Spatial localization does not require the presence of local cues. *Learning and Motivation*, 12(2), 239–260.

Moser, M. B., Trommald, M., & Andersen, P. (1994). An increase in dendritic spine density on hippocampal CA1 pyramidal cells following spatial learning in adult rats suggests the formation of new synapses. *Proceedings of the National Academy of Science of the United States of America*, 91(26), 12673–12675.

Mott, M., Robinson, D., Walden, A., Bernette, J., & Rutherford, A. (2012). Illuminating the effects of dynamic lighting on student learning. *Sage Open*, (April-June), 1–9.

Nixon, J. P., & Smale, L. (2007). A comparative analysis of the distribution of immunoreactive orexin A and B in the brains of nocturnal and diurnal rodents. *Behavioral and Brain Functions*, 3, 28.

Novak, C. M., Harris, J. A., Smale, L., & Nunez, A. A. (2000). Suprachiasmatic nucleus projections to the paraventricular thalamic nucleus in nocturnal rats (*Rattus norvegicus*) and diurnal nile grass rats (*Arviacanthis niloticus*). *Brain Research*, 874(2), 147–157.

Okamoto, Y., & Nakagawa, S. (2015). Effects of daytime light exposure on cognitive brain activity as measured by the ERP P300. *Physiology & Behavior*, 138, 313–318.

Ostroff, L. E., Fiala, J. C., Allwardt, B., & Harris, K. M. (2002). Polyribosomes redistribute from dendritic shafts into spines with enlarged synapses during LTP in developing rat hippocampal slices. *Neuron*, 35(3), 535–545.

Patro, N., Kumar, K., & Patro, I. (2013). Quick Golgi method: modified for high clarity and better neuronal anatomy. *Indian Journal of Experimental Biology*, 51(9), 685–693.

Peyron, C., Tighe, D. K., van den Pol, A. N., de Lecea, L., Heller, H. C., Sutcliffe, J. G., & Kilduff, T. S. (1998). Neurons containing hypocretin (orexin) project to multiple neuronal systems. *Journal of Neuroscience*, 18(23), 9996–10015.

Polich, J., & Geisler, M. W. (1991). P300 seasonal variation. *Biological Psychology*, 32(2–3), 173–179.

Pyter, L. M., Reader, B. F., & Nelson, R. J. (2005). Short photoperiods impair spatial learning and alter hippocampal dendritic morphology in adult male white-footed mice (*Peromyscus leucopus*). *Journal of Neuroscience*, 25(18), 4521–4526.

Ramanathan, C., Nunez, A. A., & Smale, L. (2008). Daily rhythms in PER1 within and beyond the suprachiasmatic nucleus of female grass rats (*Arvicanthis niloticus*). *Neuroscience*, 156(1), 48–58.

Riemersma-van der Lek, R. F., Swaab, D. F., Twisk, J., Hol, E. M., Hoogendijk, W. J., & Van Someren, E. J. (2008). Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *Journal of American Medical Association*, 299(22), 2642–2655.

Rodriguez, A., Ehlenberger, D. B., Dickstein, D. L., Hof, P. R., & Wearne, S. L. (2008). Automated three-dimensional detection and shape classification of dendritic spines from fluorescence microscopy images. *PLoS One*, 3(4), e1997.

Royer, M., Ballentine, N. H., Eslinger, P. J., Houser, K., Mistrick, R., Behr, R., & Rakos, K. (2012). Light therapy for seniors in long term care. *Journal of American Medical Directors Association*, 13(2), 100–102.

Ruger, M., Gordijn, M. C., Beersma, D. G., de Vries, B., & Daan, S. (2006). Time-of-day-dependent effects of bright light exposure on human psychophysiology: Comparison of daytime and nighttime exposure. *American Journal of Physiology, Regulatory Integrative and Comparative Physiology*, 290(5), R1413–R1420.

Rybak, Y. E., McNeely, H. E., Mackenzie, B. E., Jain, U. R., & Levitan, R. D. (2006). An open trial of light therapy in adult attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*, 67(10), 1527–1535.

Schwartz, M. D., & Smale, L. (2005). Individual differences in rhythms of behavioral sleep and its neural substrates in Nile grass rats. *Journal of Biological Rhythms*, 20(6), 526–537.

Scoville, W. B., & Milner, B. (2000). Loss of recent memory after bilateral hippocampal lesions. 1957. *The Journal of Neuropsychiatry & Clinical Neuroscience*, 12(1), 103–113.

Segal, M. (2017). Dendritic spines: Morphological building blocks of memory. *Neurobiology of Learning and Memory*, 138, 3–9.

Smale, L., Lee, T., & Nunez, A. A. (2003). Mammalian diurnality: some facts and gaps. *Journal of Biological Rhythms*, 18(5), 356–366.

Smarr, B. L., Jennings, K. J., Driscoll, J. R., & Kriegsfeld, L. J. (2014). A time to remember: The role of circadian clocks in learning and memory. *Behavioral Neuroscience*, 128(3), 283–303.

Spacek, J., & Harris, K. M. (1997). Three-dimensional organization of smooth endoplasmic reticulum in hippocampal CA1 dendrites and dendritic spines of the immature and mature rat. *Journal of Neuroscience*, 17(1), 190–203.

Tsien, J. Z., Huerta, P. T., & Tonegawa, S. (1996). The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. *Cell*, 87(7), 1327–1338.

Tsujino, N., & Sakurai, T. (2009). Orexin/hypocretin: a neuropeptide at the interface of sleep, energy homeostasis, and reward system. *Pharmacological Reviews*, 61(2), 162–176.

Tyler, W. J., & Pozzo-Miller, L. (2003). Miniature synaptic transmission and BDNF modulate dendritic spine growth and form in rat CA1 neurones. *The Journal of Physiology*, 553(Pt 2), 497–509.

Vandewalle, G., Balteau, E., Phillips, C., Degueldre, C., Moreau, V., Sterpenich, V., . . . Maquet P. (2006). Daytime light exposure dynamically enhances brain responses. *Current Biology*, 16(16), 1616–1621.

Vandewalle, G., Gais, S., Schabus, M., Balteau, E., Carrier, J., Darsaud, A., . . . Maquet, P. (2007a). Wavelength-dependent modulation of brain responses to a working memory task by daytime light exposure. *Cerebral Cortex*, 17(12), 2788–2795.

Vandewalle, G., Maquet, P., & Dijk, D. J. (2009). Light as a modulator of cognitive brain function. *Trends in Cognitive Sciences*, 13(10), 429–438.

Vandewalle, G., Schmidt, C., Albouy, G., Sterpenich, V., Darsaud, A., Rauchs, G., . . . Dijk D. J. (2007b). Brain responses to violet, blue, and green monochromatic light exposures in humans: prominent role of blue light and the brainstem. *PLoS One*, 2(11), e1247.

Viola, A. U., James, L. M., Schlangen, L. J., & Dijk, D. J. (2008). Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scandinavian Journal of Work, Environment & Health*, 34(4), 297–306.

Vorhees, C. V., & Williams, M. T. (2006). Morris water maze: procedures for assessing spatial and related forms of learning and memory. *Nature Protocols*, 1(2), 848–858.

Walker, M. P., & Stickgold, R. (2006). Sleep, memory, and plasticity. *Annual Review of Psychology*, 57, 139–166.

Yamadera, H., Ito, T., Suzuki, H., Asayama, K., Ito, R., & Endo, S. (2000). Effects of bright light on cognitive and sleep-wake (circadian) rhythm disturbances in Alzheimer-type dementia. *Psychiatry and Clinical Neuroscience*, 54(3), 352–353.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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