Reward effects of light

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Chapter 1: General Introduction

First indications of the links between light and mood

A 1984 seminal report by Rosenthal and colleagues was the first scholarly description of Seasonal Affective Disorder (SAD) (Rosenthal et al., 1984). The report indicated that waning day length during fall and winter precipitates symptoms of depression in the patients described, which subside when days lengthen in spring and summer (Rosenthal et al., 1984). SAD prevalence is high in countries outside the tropics (e.g. ~1% in the USA), shows higher prevalence with higher latitude (e.g. 2-3% in Canada) and can be quite common in northern latitudes (up to 10%) (Kurlansik et al., 2012; Nunn et al., 2016).

In 1984, bright light therapy (BLT) was also discovered as an effective SAD treatment (Rosenthal et al., 1984). BLT consists in exposing the eyes to light of appropriate intensity, duration and at appropriate times of day; and results in amelioration of affective and physical symptoms of SAD (Rosenthal et al., 1984). Since then, SAD has been the most well-known disorder that has an increased probability to emerge at a certain time of the year and is treated by ambient light modifications (Rosenthal et al., 1984). Humans have anatomical pathways that convert light signals into physiological cues (Wehr et al., 2001). However, the specific pathophysiological brain substrates of SAD are mostly unknown, as are the mechanisms by which BLT has a therapeutic effect.

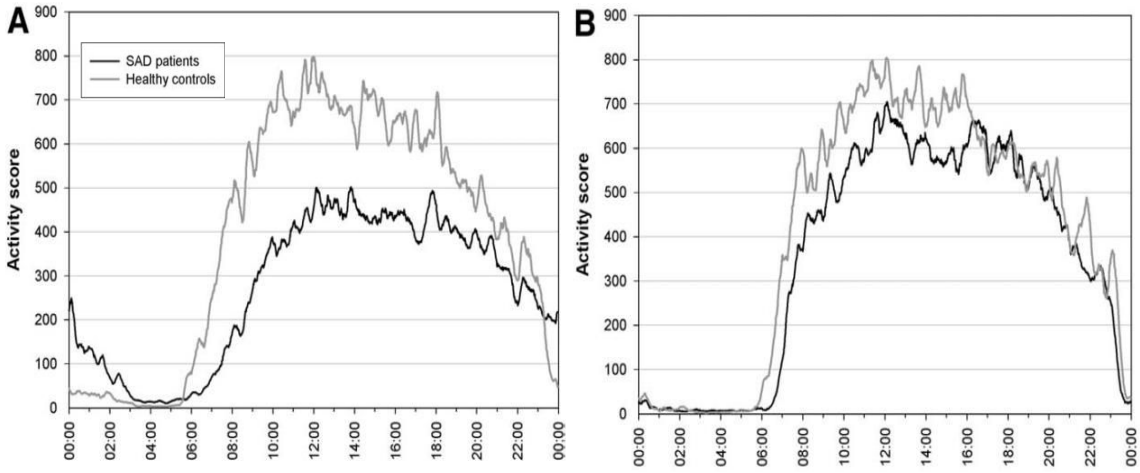

Figure 1. 24h Actigraphic measurements (locomotor activity) of 17 patients with Seasonal Affective Disorder (SAD) and 17 healthy control subjects before (A) and after 4 weeks (B) of treatment with bright light therapy (BLT). The recordings display delayed sleep and activity onset phase in patients with SAD as compared to controls, which is greatly resolved by 4 weeks under BLT. BLT was administered at home as 30 mins of 10,000 lux between 7:00 and 9:00 am, for four weeks during the fall-winter season. Taken from (Winkler et al., 2005).

The prevailing explanation of the pathophysiology of SAD is the phase shift hypothesis. The phase shift hypothesis proposes that, during winter, light does not adequately entrain the circadian clock resulting in delays of the sleep-wake cycle and other physiological rhythms with respect to the external light-dark cycle (Ksendzovsky et al., 2017). The resulting phase shift is evidenced in the motor activity (see figures 1A and 2), and induces changes on mood and cognition (LeGates et al., 2015). Moreover, the prevailing hypothesis of how BLT exerts its effects is the correction of the circadian phase shift to which SAD has been related (Pail et al., 2011).

Mood has also been found to be disrupted in mice exposed to aberrant light schedules (e.g. alternating faster light-dark cycles, jet lag or dim light at night models) (Bedrosian et al., 2011; LeGates et al., 2013; Yamaguchi et al., 2014). Indeed, an unconventional 3.5 h of light and 3.5 h of dark cycle also disrupts mood, with the added feature that of causing no changes in the circadian system, sleep amount or sleep architecture (LeGates et al., 2012). Hence, light can have effects on mood and cognition not mediated by the circadian clock. As a result, two pathways account for the effects of light on mood: an indirect pathway in which inappropriate circadian rhythm entrainment by light disturbs sleep and circadian phase and these in turn disturb mood and cognition; and a direct pathway in which light signals directly reach structures of the reward system from the retina and thereby influence mood and cognition (see figure 2) (LeGates et al., 2013).

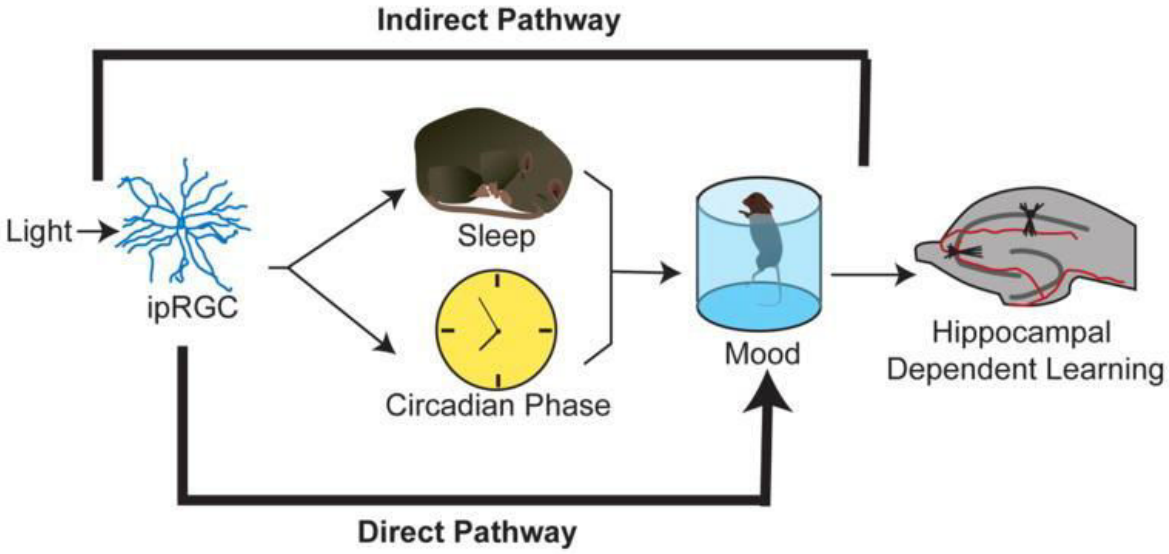

Figure 1. Model of the direct and indirect influences of light on mood and cognition. Light can regulate mood and learning by modulating sleep and circadian rhythms (indirect path), or affect mood without disrupting sleep or causing circadian arrhythmicity (direct pathway). ipRGC (intrinsic photosensitive retinal ganglion cells). Taken from (LeGates et al., 2014)

BLT was also demonstrated efficacious in diminishing complaints outside of SAD, like in non-seasonal depression and primary insomnia (Al-Karawi and Jubair, 2016; Even et al., 2008; Maanen et al., 2016). Depression and insomnia also present with mood disturbance, and the efficacy of BLT in these disorders further suggests that light has direct effects on mood. However, studies of the effect of light on mood have mostly limited to maximizing effectiveness of BLT in SAD (Burgess et al., 2004; LeGates et al., 2015, 2013; Wirz-justice et al., 1993) or depression and insomnia (Al-Karawi and Jubair, 2016; Maanen et al., 2016). These studies have focused on manipulating parameters such as time of exposure, duration, light intensity and light spectrum composition. In contrast, the mechanisms by which light induces these effects are neglected.

Intrinsically photosensitive Retinal Ganglion Cells (ipRGCs) and non-image-forming effects of light

Similarly to mood, other biometric variables also seem to be influenced by light and have been found to be mediated by light information from the retina. In mammals, the retina detects light using specialized photoreceptor cells. Rods and cones are the “classical photoreceptors” primarily

responsible for image-forming vision. A third class of photoreceptors, called intrinsically photosensitive retinal ganglion cells (ipRGCs, see figure 3a and 3c), perform non-image-forming functions. The photopigment melanopsin which ipRGCs allows them to be intrinsically photosensitive with maximal sensitivity to blue light (460-480 nm) (LeGates et al., 2015).

ipRGCs have projections from the retina to the brain (Hattar et al., 2002; Provencio et al., 2000). Key areas that ipRGCs directly project to include the suprachiasmatic nucleus (SCN, see figure 3b), which contains the principal circadian clock, and the ventrolateral preoptic area (VLPO), which regulates sleep (LeGates et al., 2015). Indeed, ipRGCs transduce information on environmental light intensity to signal non-image-forming (NIF) effects of light. NIF effects have been found to modulate alertness (Cajochen et al., 2000), circadian behavior (Boivin et al., 1996) and sleep (Dijk et al., 1991), and likely make up the substrate by which light indirectly affects mood.

Besides the circadian and sleep-related projections, ipRGCs also project to targets involved in reward processing such as the amygdala and the dorsal border of the lateral habenula (LeGates et al., 2015). Human brain imaging studies of light exposure have shown that blue light influences the amygdala by increasing the temporal dependency of neuronal activation patterns with other brain areas during emotional processing – its functional connectivity (see Heuvel and Pol, 2010; Vandewalle et al., 2010). ipRGCs most likely play a role in both the direct and indirect pathways by which light influences mood. However, elucidating downstream mechanisms by which light influences mood has been relatively elusive.

Study of the effects of light on mood via indirect and direct pathways

The indirect influence of light on mood through circadian and sleep systems has been studied in human and animal models. In a study on social interactions in people with mild seasonal mood complaints, high intensity light exposure improved mood, reduced quarrelsome behaviors, and promoted more agreeable behaviors (aan het Rot et al., 2008). Animal models allow the study of biochemical changes on brain structures entailed by exposure to winter-like photoperiodic conditions, e.g. shortened day-length and/or lower daylight intensity (Workman and Nelson, 2011). Similarly, the rescue mechanisms of light exposure may also be studied. However, while most animal models have used nocturnal rodents (e.g., mice, rats; which have aversive responses to light), models using diurnal rodents are slowly being introduced as promising and viable models (Workman and Nelson, 2011). The use of diurnal animals is crucial for modelling underlying mechanisms of the reward effects of light because it allows circumventing aversive responses to light characteristic of nocturnal rodents.

Beyond comparing effectiveness of light as BLT vs. other modalities, few laboratory imaging studies have focused on comparing human brain responses to lights and have focused at comparing the responses to *different wavelengths* (Vandewalle et al., 2009). Studies on the effect of light *intensity* on the reward system in humans have mostly been confined to the evaluation of mood ratings. Several laboratory studies demonstrated acute effects of environmental light intensity on the evaluation of affect elicited by stimuli (Revell et al., 2006; Vandewalle et al., 2011, 2010). Only few studies addressed the effect of light intensity on mood ratings in naturalistic environments (aan het Rot et al., 2008; Dumont and Beaulieu, 2007). This modality could benefit from the incorporation of measures to facilitate the study of mood as an output of the reward system. Two such measures that have come to attention recently are wanting and liking (Berridge and Kringelbach, 2013). Utilizing these

measures may prove useful in determining the impact of light on mood beyond the resolution of disease symptoms.

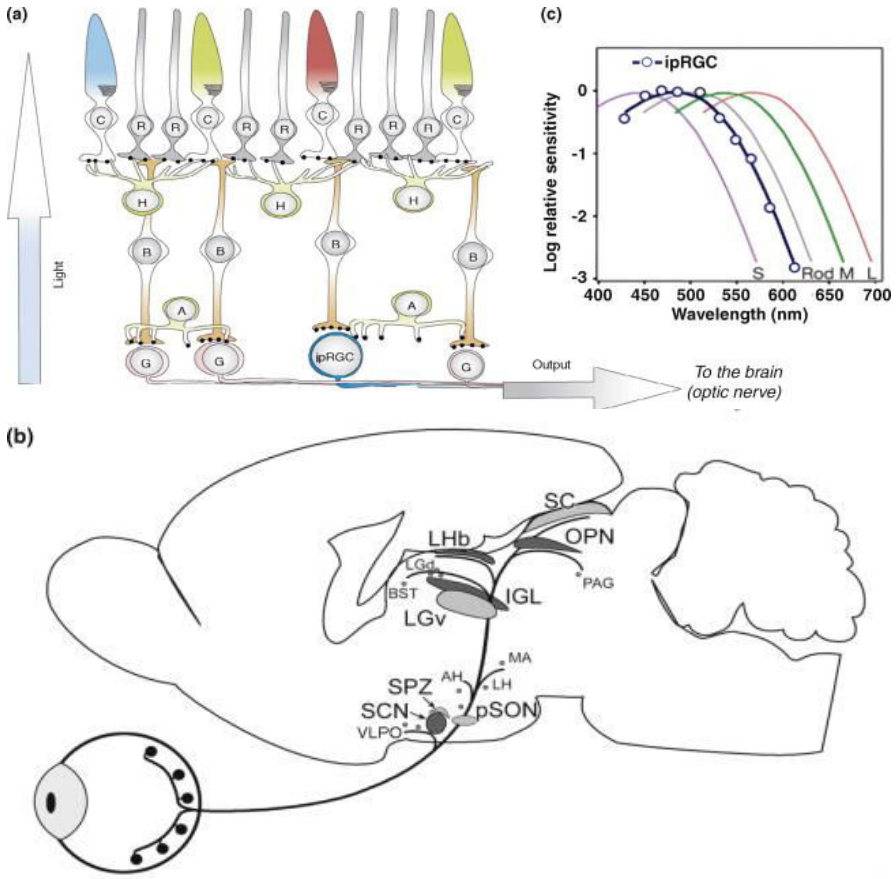

Figure 3. Photo-reception in mammals. The schematics show (a) how light passes through the ganglion cell layer before reaching rods (R) and cones (C). Light information is transferred by the optic nerve composed of ganglion cells axons. The photopigment melanopsin is expressed in a subset of intrinsically photosensitive retinal ganglion cells (ipRGCs), which allows them to have intrinsic responses to light. (b) ipRGCs projections to the brain include hypothalamic areas such as the suprachiasmatic nucleus (SCN), the ventro-lateral preoptic nucleus (VLPO) and the lateral hypothalamus (LH). ipRGCs also target the limited border of the lateral habenula (LHb), a relay site between limbic and striatal areas and the midbrain, and the amygdala (MA), involved in emotion regulation. (c) Wave-length sensitivities of cones most sensitive to short (S), medium (M), and long wavelength light (L), as well as that of rods ( ), and melanopsin-expressing ipRGCs ( ). IpRGCs have a maximum sensitivity around 480 nm pSON, peri-supraoptic nucleus; SPZ, subparaventricular zone; AH, anterior hypothalamus; MA, medial amygdala; LGv and LGd, ventral and dorsal region of the lateral geniculate nucleus; BST, bed nucleus of stria terminalis; IGL, intergeniculate leaflet; PAG, periaqueductal gray; SC, superior colliculus; OPN, olivary pretectal nucleus (Vandewalle et al., 2009).

Finally, one of the explanations that could potentially unify these direct and indirect effects of light (e.g. even in the emergence of SAD) is the pathophysiological model of hyperarousal, the prevailing pathophysiological explanation of insomnia (Riemann and Voderholzer, 2003). The hyperarousal framework might also have validity in depression as depression is a risk factor for insomnia and vice versa (Riemann and Voderholzer, 2003). The hyperarousal pathophysiological model states that these disorders result from central and peripheral (autonomic) nervous system activation which interferes with the natural disengagement from the environment (Levenson et al.,

2015; Riemann and Voderholzer, 2003). However, the role of light in hyperarousal has not been considered in the framework. The hyperarousal model might indeed be an overarching theme connecting depressive disorders and insomnia, as about 13% of people with insomnia develop depression within a year (Baglioni et al., 2010). Moreover, the difficulty initiating or maintaining sleep (for at least 1 month) is a core symptom in the disorder primary insomnia and a secondary one amongst the criteria for depression, including SAD (Berk, 2009). Insomnia can exist years before the onset of depression (McCrae and Lichstein, 2001), may herald relapses in patients with recurrent depression (Perlis et al., 1997) and has been suggested as a "comorbid" condition to depression. The efforts described in this dissertation may further elucidate this framework and contribute to improvements in the diagnosis and treatment (e.g. via light exposure) of these diseases which are among the most prevalent and burdening health concerns (Cuijpers et al., 2012).

Aims of this dissertation

As part of the Neurotime Project "Reward Effects of Light" and using a translational research approach this thesis proposed a framework to gain further insight into effects of light on mood and the behavioral and central physiological mechanisms by which they might be entailed. This endeavor is multidimensional and aimed to circumvent the limitations of previous methods of study.

The aims of this dissertation were:

- Evaluate the potential effects of light on behavior and brain physiology using the diurnal rodent *Arvicanthis ansorgei* exposed to a winter-like photoperiod (short daylength with lower light intensity).
- Elucidate immediate effects of light on subjective affective variables in naturalistic settings in a healthy population.
- Investigate how subjective affective variables may differ in people with insomnia and are modulated by environmental light exposure.

In **Chapter 2**, *A. ansorgei* subjects (see appendix) were tested under control photoperiodic conditions (12:12h light/dark [LD] cycle), under winter-like photoperiodic conditions (LD8:16h with reduced light intensity) and after rescue using daily light pulses early in the morning or late in the day. They were studied using actigraphy to evaluate locomotor activity rhythms, measures of dopaminergic activity were obtained from two forebrain reward structures (caudate-putamen and nucleus accumbens) and the expression of clock genes in the SCN were measured. In this study, we aimed to characterize circadian features induced by winter-like photoperiodic conditions and gain insight into the dopaminergic changes that accompany them, and later on characterize the behavioral and dopaminergic brain changes induced by light pulses at two different times of day (early morning vs. late day).

Chapter 3 describes an experiment conducted to evaluate subjective affect measures across seven days in a young healthy population and how they are modulated by environmental light. A combination of environmental sampling and light sensors (see appendix) were utilized with the aim of determining liking and wanting in trials across the day and their correlation with light level fluctuations under natural everyday life setting.

Chapter 4 featured a similar design as that described for the experiment in Chapter 3 but it was performed in a population with insomnia and age- and sex-matched controls. The aim of this study

was to evaluate wanting and liking in insomnia and the proposed ameliorative effect that light could have on deficiencies of hedonic capacity, a hypothesis of how the influence of light on mood may figure in the hyperarousal framework.

In **Chapter 5**, the findings of each chapter are discussed in the context of the aims of this project, in order to draw conclusions regarding the non-image forming effects of light on mood and the mechanisms by which light induces a rewarding effect.

Chapter 2: Light rescues circadian behavior and brain dopamine abnormalities in diurnal rodents exposed to a winter-like photoperiod

Light rescues circadian behavior and brain dopamine abnormalities in diurnal rodents exposed to a winter-like photoperiod

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Abstract

Seasonal affective disorder (SAD), beyond mood changes, is characterized by alterations in daily rhythms of behavior and physiology. The pathophysiological conditions of SAD involve changes in day length and its first-line treatment is bright light therapy. Animal models using nocturnal rodents have been studied to elucidate the neurobiological mechanisms of depression, but might be ill suited to study the therapeutic effects of light in SAD since they exhibit light-aversive responses. Here *Arvicanthis ansorgei*, a diurnal rodent, was used to determine behavioral, molecular and brain dopamine changes in response to exposure to a winter-like photoperiod consisting of a light–dark cycle with 8 h of light, under diminished light intensity, and 16 h of darkness. Furthermore, we evaluated whether timed-daily bright light exposure has an effect on behavior and brain physiology of winter-like exposed animals. *Arvicanthis* under a winter-like condition showed alterations in the synchronization of the locomotor activity rhythm to the light–dark cycle. Moreover, alterations in day–night activity of dopaminergic neurotransmission were revealed in the nucleus accumbens and the dorsal striatum, and in the day–night clock gene expression in the suprachiasmatic nucleus. Interestingly, whereas dopamine disturbances were reversed in animals exposed to daily light at early or late day, altered phase of the daily rhythm of locomotion was reverted only in animals exposed to light at the late day. Moreover, *Per2* gene expression in the SCN was also affected by light exposure at late day in winter-like exposed animals. These findings suggest that light induces effects on behavior by mechanisms that rely on both circadian and rhythm-independent pathways influencing the dopaminergic circuitry. This last point might be crucial for understanding the mechanisms of non-pharmacological treatment in SAD.

Introduction

Seasonal affective disorder (SAD) is a subset of depressive symptoms which correlate with seasonal fluctuations in environmental light (Rosenthal et al. 1984). SAD symptomatology feature changes in circadian rhythmicity (e.g., sleep, feeding and activity) which are modulated by light. Indeed, bright light therapy (BLT) is a useful treatment of SAD and other psychiatric disorders (Rosenthal et al. 1984; Lieverse et al. 2011; Terman and Terman 2005). BLT efficacy is dependent on variables such as light intensity, wavelength, duration and timing of exposure (Wirz-Justice et al. 1993; LeGates et al. 2014). However, a little is known about the brain changes that anticipate or are secondary to the light effects on mood.

The monoaminergic hypothesis, which proposes that mood disorders result through neurotransmitter system imbalances, has led to various therapies acting mostly on the serotoninergic (5-HT) system (Neumeister et al. 2001; Stahl et al. 2013). While serotoninergic targets in the frontal cortex are critical therapeutic mediators, other reward mediating areas such as the nucleus accumbens (NAcc) and ventral tegmental area (VTA), important in dopaminergic (DA) transmission, are promising therapeutic targets that might have been overlooked (Russo and Nestler 2013). DAergic transmission from the VTA to NAcc mediates behavioral responses to natural and non-natural rewards, motivation and motor functions (Berridge and Kringelbach 2013). In major depression, lower motivation and motor activity, and DAergic changes are classical symptoms (Russo and Nestler 2013; Opmeer et al. 2010). Hence, DA transmission might also be altered in SAD patients.

DA activity shows circadian and seasonal variations, which could be a result of the influence of solar time on the circadian clock in the suprachiasmatic nucleus (SCN) (Hood et al. 2010; Mendoza and Challet 2014; Verwey et al. 2016; Eisenberg et al. 2010; Diehl et al. 1994). Some studies have reported a possible influence of photoperiodic conditions and light in the brain DAergic system, which can be correlated with emotional states (Neumeister et al. 2001; Tsai et al. 2011; Cawley et al. 2013). However, DAergic changes in SAD and the effects of light on DA brain content remain to be elucidated. Previously, animal models in this field relied on nocturnal species such as rats and mice which have aversive responses to light (Tavolaro et al. 2015; Deibel et al. 2014). Diurnal species such as the grass rat *Arvicanthis niloticus* display acute behavioral responses to light (Shuboni et al. 2012). They, together with other diurnal rodents, have proven useful to investigate depression-like behaviors under winter-like lighting conditions (Deats et al. 2015; Krivisky et al. 2011; Leach et al. 2013a, b; Ashkenazy-Frolinger et al. 2010).

Here, a series of experiments were designed to elucidate behavioral and central changes induced by winter-like photoperiods in a diurnal rodent, as well as the possible rescue effects of bright light at two different times at day (early day vs. late day). Grass rats (*Arvicanthis ansorgei*) were exposed to winter-like photoperiodic conditions, consisting of shorter light phases (8 h) with lower light intensity around the 24 h. The effects of these conditions were studied on rhythmic behavior, DA content in the dorsal striatum (caudate–putamen; CP) and NAcc and clock gene expression in the SCN. Furthermore, the effects of daily light pulses at the early vs. late day on animals exposed to winter-like photoperiod were also studied in the aforementioned conditions. Our data reveal that a winter-like condition in the diurnal rodent *Arvicanthis ansorgei* alters daily rhythms of locomotion, DA content in the forebrain and clock gene expression in the SCN. More important, whereas DAergic alterations were rescued when animals are exposed to daily light at either early or late day, circadian phase was only recovered in animals exposed to light at the late day.

Materials and methods

Animal care and handling

This study was conducted using Sudanian unstriped grass rats (*Arvicanthis ansorgei*) born and reared in animal facilities in Strasbourg (Chronobiotron UMS 3415). Animals were housed in regulated temperature (23 ± 1 °C) in individual cages under a 12/12 h light–dark (LD) cycle and provided *ad libitum* access to food (Ref. 105, SAFE, 89290, Augy, France) and tap water, unless otherwise indicated. Animal handling was conducted in accordance with the Guide for the Care and Use of Laboratory Animals (NIH Pub. No. 86-23, revised 1985) and the French Department of Agriculture (License no. 67-378 to J.M.).

Experimental design

Male adult *Arvicanthis*, weighing 191.1 ± 5.3 g (5 months of age) at the beginning of the experiment, were acclimatized in single cages under a 12/12 h LD cycle (light at 150 lux at cage level, dark at < 5 lux dim red light), lights on at 7:00 h [defined as Zeitgeber Time (ZT0)], and lights off at 19:00 h for 3 weeks. Daily locomotor activity rhythms were measured throughout the whole experiment.

Thereafter, animals were exposed to a winter-like photoperiod condition with a LD8/16h with reduced light intensity during day phase (45 lux), lights on at 9:00 h (redefined ZT0) and lights off at 17:00 h (ZT8) for 6 weeks. Light intensity was measured by handheld luxometer at the base of the animal cage. Then animals were divided in two groups: a winter-like + light exposure at ZT0 group (early day, $n = 12$) and a winter-like + light exposure at ZT7 (late day, $n = 12$) group. The bright light exposed animals received a 45 min light pulse of 150 lux starting at ZT0 (early day) or ZT7 (late day) and an additional 15 min pulse of 1900 lux at cage level, finishing with lights off at ZT1 (1 h after lights on) or ZT8 (last hour of the light phase), respectively, for 4 weeks. The 15 min light pulse was administered with an overhead lamp housing two cool white fluorescent bulbs (TL-D36W/965; Philips, Somerset, NJ) mounted on a custom-made aluminum frame whose height could be adjusted to vary light intensity.

Locomotor activity recordings

Infrared captors placed on the top of each cage logged locomotor activity counts which were stored in a computer using CAMS (Circadian Activity Monitoring System, Lyon France) software. Actograms and average waveforms were constructed using ClockLab software (Actimetrics, Evanston, IL, USA). Quantified general activity parameters included 24 h mean activity profiles for animals under each photoperiod and the phase angle of entrainment of locomotor activity rhythms, defined as the time of activity onset relative to the time of lights-on. To evaluate differences in the phase angle of entrainment (activity onsets and offsets) between different conditions (LD12/12h vs. winter-like vs. winter-like + light), we compared the mean of the activity onsets and offsets per each experimental condition. Moreover, we determine the robustness of behavioral rhythms analyzing the amplitude of rhythm under each experimental condition using the fast Fourier transform, which estimates the relative power of 24 h period rhythms in comparison with other periodicities in the time series (ClockLab software, Actimetrics, Evanston, IL, USA).

Biochemical analysis

Brains were recovered and frozen in methylbutane at − 30 °C, and stored at − 80 °C for posterior analysis. Samples from the dorsal striatum (caudate–putamen, CP) and NAcc were punched out from 1-mm thick brain slices under a cryostat using a 2.5-mm-diameter aluminum tube and placed in Eppendorf tubes, stored at − 80 °C and analyzed within 4 weeks of collection. A mobile phase consisting of 50 mM citric acid, 40 mM Na_2HPO_4, 0.8 mM EDTA, 0.3 mM octanesulfonic acid and 1% methanol, dissolved in ultrapure water 0.22 µm was filtered, degassed. Tissue samples were individually homogenized in 150 µl of mobile phase by sonication. Samples were kept at 4 °C during preparation and before sampling via autosampler (Triathlon, Spark, Emmen, the Netherlands). DA and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) were detected with a HPLC system using an amperometric electrochemical detector (Decade Antec, Leyden, the Netherlands). The electrochemical flowcell VT-03 was an Ag/AgCl (with saturated KCl) versus glassy carbon electrode configuration. Potential between working and auxiliary electrode was set at 0.8V for detection. The temperature for the oven including cell detection and column was maintained at 30 °C. The system featured a high-pressure pump (LC-10AD, Shimadzu, Kyoto, Japan). Each 20 µl sample was injected on 750-mm length, 4.6-mm internal diameter, 3-µm C18 columns (Ultrasphere ODS, Beckman, Fullerton, CA, USA). Isocratic separation flow rate was kept at 0.5-ml/min. Every analysis lasted 60 min. DA and DOPAC (Sigma-Aldrich) standard solutions were prepared in 10 mM HCl at 4 °C and protected from light. Appropriate dilutions in the mobile phase were used to obtain a 3-point curve with good correlation rate for each standard. Retention times for our chromatographic conditions were 7.5 min for DA and 10.9 min for DOPAC. Values were calculated using Azur acquisition software v4.5 (Datalys, St Martin d'Hères, France). Results were given as pg/mg of total protein after protein dosage with the Bradford method. Furthermore, we analyzed the DOPAC/DA ratio commonly used as an index of DA turnover (Bagchi 1998).

In situ hybridization

After recovery of samples containing the dorsal striatum and NAcc for HPLC analysis, caudal part of brains was sectioned at the level of the SCN. Coronal 18 µm SCN slices were obtained with a cryostat. In situ hybridization of *Per2, Bmal1* and Vasopressin (*Avp*) mRNA expression was performed using riboprobes of *Per2* (kindly provided by Dr. H. Okamura, Kyoto University, Japan), *Bmal1* and *Avp* (kindly provided by Dr. H. Dardente, Tours University, France). Antisense RNA probes were generated with an *in vitro* transcription kit (Maxiscript; Ambion, Austin, TX, USA). Hybridization was carried out as described previously (Mendoza et al. 2012). Slices and radioactive standards were exposed to an autoradiographic film (Biomax MS-1 Kodak, Sigma-Aldrich, St Louis, MO, USA). Quantitative analysis of the autoradiograms was performed using the ImageJ software (W. Rasband, National Institutes of Health, Bethesda, MD, USA). The optical density of the whole SCN was measured and relative optical density was determined by subtracting the background intensity (measured in the anterior hypothalamic area) from the signal for each animal. Left and right SCN sided relative optical densities were averaged.

Statistical analysis

Data were compared using either one- or two-way ANOVA for independent and repeated measures using SigmaPlot 13.0 software (Systat Software, Inc.). When significant main effects were obtained ($p < 0.05$), differences between groups at each condition were tested using the LSD Fisher post hoc test.

Results

Effects of daily light exposure at the early or late day on daily rhythms of behavior of *Arvicanthis* exposed to winter-like conditions

Arvicanthis exposed to control LD12/12h photoperiod display stable activity rhythms with locomotion predominantly during day time (Fig. 1a, c), and with an activity onset anticipating lights on (Fig. 1b, d, 1.23 ± 0.09 h before ZT0). Once exposed to a winter-like photoperiod LD8/16h, *Arvicanthis* displayed an activity phase advance (Fig. 1a–d 2.08 ± 0.16 h before ZT0) characterized by earlier onset compared to the control LD12/12h condition (Fig. 1d, $F_{(2,35)} = 12.81$; $p < 0.001$). This change in phase was also observed in activity offsets (Fig. 1a–d − 0.47 ± 0.20 h after lights off, $F_{(2,35)} = 12.5$; $p < 0.001$). No effects of winter-like conditions on the amplitude of behavioral rhythms were observed (Fig. 1c, $F_{(2,35)} = 1.05$; $p = 0.3$).

Then, we evaluated the effects of 1 h daily bright light exposure at the early day (ZT0) on daily rhythms behavior in animals exposed to winter-like photoperiods. The phase advance induced by LD8/16h photoperiod was not delayed in animals exposed to 1 h of light from ZT0 to ZT1 (Fig. 1a–d; post hoc $p = 0.09$).

In *Arvicanthis* from the winter-like + light ZT7 group, daily rhythms of locomotion under control LD12/12h photoperiod display stable and diurnal activity rhythms (Fig. 2a, c), and with an activity onset anticipating lights on (Fig. 2b, d, 1.46 ± 0.1 h before ZT0). Similar to *Arvicanthis* from the previous group (Fig. 1), the exposure to a winter-like photoperiod LD8/16h lead in an activity phase advance characterized by earlier onset (Fig. 2a–d, 2.01 ± 0.12 h before ZT0) and offset (− 0.40 ± 0.24 h after lights off) compared to the control LD12/12h condition (Fig. 2d, onsets, $F_{(2,35)} = 2.92$; $p < 0.001$; offsets, $F_{(2,35)} = 23.21$; $p < 0.001$). The amplitude of behavioral rhythms was not affected by the winter-like conditions (Fig. 2c, $p = 0.840$).

However, when winter-like exposed *Arvicanthis* received daily light pulses at the late day (from ZT7 to ZT8), activity onsets and offsets were delayed and rescued in comparison to the winter-like condition (Fig. 2a–d; post hoc $p < 0.001$). Moreover, the amplitude of the daily locomotor activity rhythms was significantly increased in animals exposed to daily light at ZT7 (Fig. 2c; post hoc $p = 0.003$).

Daily light exposure effects on brain DAergic activity of winter-like exposed animals

We asked whether a winter-like photoperiod alters the day–night difference in the DA content and turnover as described by DOPAC/DA ratios measured by HPLC. For NAcc, a significant group effect for DA content ($F_{(3,37)} = 12.58$; $p < 0.001$) and its metabolite DOPAC ($F_{(3,37)} = 5.59$; $p = 0.004$) was revealed, showing higher levels of both molecules in winter-exposed animals at night time (ZT19), in comparison to control LD12/12h *Arvicanthis* (Table 1). When we analyzed the DOPAC/DA ratio, the ANOVA indicates a significant effect for the time factor ($F_{(1,37)} = 7.67$; $p = 0.01$), showing a downregulation on DA turnover by the winter-like condition (Fig. 3a). In the CP, there was a

significant difference for the group condition for both DA ($F(3,36) = 12.58$; $p = 0.006$) and DOPAC content($F_{(3,36)} = 3.01$; $p = 0.04$), with higher levels in the winter-like group than in control LD12/12h animals at night (ZT19) (Table 1). The DOPAC/DA ratio in the CP showed a significant difference for the factor time ($F_{(1,36)} = 6.58$; $p = 0.01$) revealing a day-time difference with significantly higher DA turnover at ZT19 than ZT7 for the control group, and with no day–night difference under winter-like conditions (Fig. 3b).

The effects of light on DA metabolism showed significant changes on the content of DA and DOPAC in the NAcc at night time (ZT19) (post hoc $p < 0.05$), in comparison to winter-like *Arvicanthis* (Table 1). When we analyzed the DOPAC/DA ratio, the ANOVA indicates a significant effect for the time factor ($F(1,37) = 7.67$; $p = 0.01$), showing a recovery of the day–night DA turnover by light at late day (ZT7; post hoc $p = 0.005$), but not at early day (ZT0), despite the statistical analyses were at the limit of significance ($p = 0.08$; Fig. 3a). In the CP, there was also an effect of light on DA and DOPAC content, similar to results in the NAcc (Table 1; post hoc $p < 0.05$). The DOPAC/DA ratio in the CP showed a significant difference for the factor time ($F_{(1,36)} = 6.58$; $p = 0.01$) revealing a day–night difference in control conditions (LD12/12h) but suppressed under winter-like conditions, and which showed a tendency to be rescued in *Arvicanthis* receiving daily light stimulation at both ZT0 or ZT7, but the post hoc analyses were not significant ($p = 0.08$; Fig. 3b).

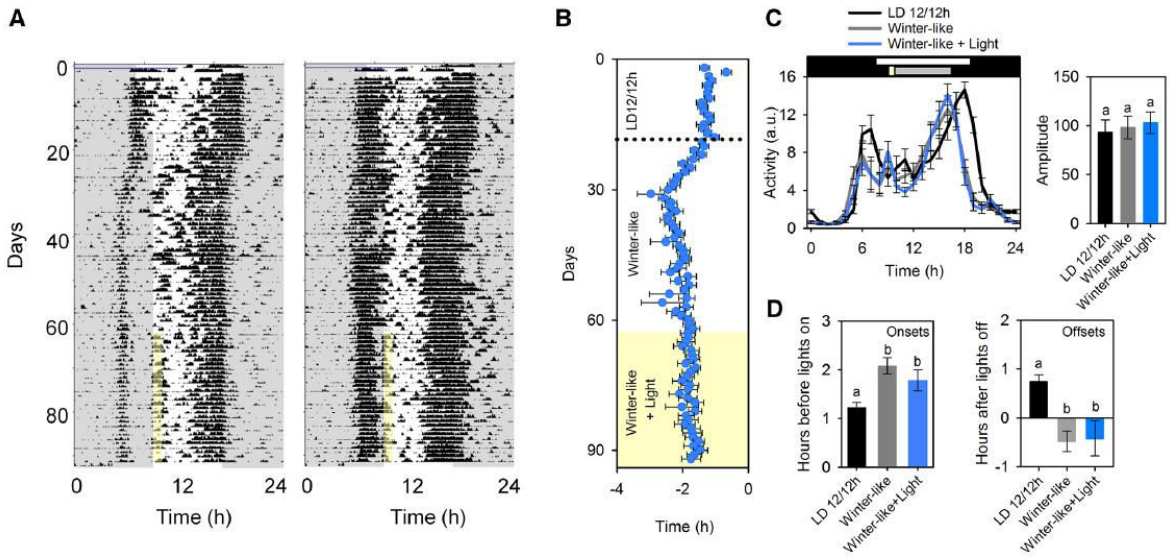

Fig. 1 Behavioral rhythms of *Arvicanthis ansorgei* under a winterlike photoperiod and exposed to daily light at the early day (ZT0). **a** Representative actograms of the rhythm of locomotor activity of animals during the whole experiment. *Arvicanthis* kept under LD12/12h conditions [12 h of light at 150 lux and 12 h of darkness, < 5 lux (gray shaded area of graph)] were later switched to winter-like LD8/16h photoperiod (8 h of light at 45 lux, and 16 h of darkness, < 5 lux), and finally animals were exposed to 1 h daily light pulses at lights on from ZT0 to ZT1 (vertical yellow bar in actograms). **B** Activity onsets averaged across each day during the whole experiment; LD12/12h, winter-like condition (dotted line) and winterlike + light (shaded yellow area). **c** Left: Daily activity profiles of animals during different experimental conditions (LD12/12h vs. winter-like vs. winter-like + light). Top bars represent the LD cycle in control conditions (black and white bars) and during winter-like (black and grey bars) and winter-like + light exposure (yellow bar). Right: Amplitude of locomotor activity rhythms at different experimental conditions. **d** Daily average onsets (hours before lights on) and offsets (hours after lights off) of activity showing a phase-advance under winter-like photoperiodic conditions which was not affect by daily light exposure at ZT0. Data are shown as the mean ± SEM. Means lacking common letters are significantly different (between groups LSD post hoc test, $p < 0.05$)

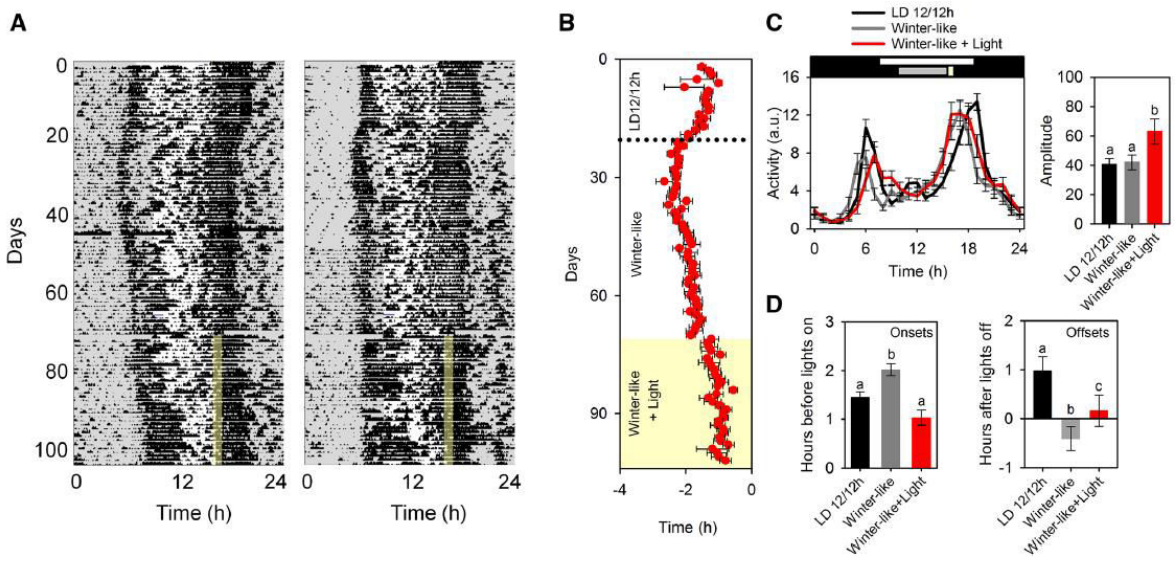

Fig. 2 Behavioral rhythms of *Arvicanthis ansorgei* under a winter-like photoperiod and exposed to daily light at the late day (ZT7). **a** Representative actograms of the rhythm of locomotor activity of animals during the whole experiment. *Arvicanthis* kept under LD12/12h conditions [12 h of light at 150 lux and 12 h of darkness, < 5 lux (gray shaded area of graph)] then to winter-like LD8/16h photoperiod (8 h of light at 45 lux, and 16 h of darkness, < 5 lux), and exposed to 1 h daily light pulses right before lights off, from ZT7 to ZT8 (vertical yellow bars). **b** Activity onsets averaged across each day during the whole experiment; LD12/12h, winter-like condition (dotted line) and winter-like + light (shaded yellow area). **c** Left: Daily activity profiles of animals during different experimental conditions (LD12/12h vs. winter-like vs. winter-like + light). Top bars represent the LD cycle in control conditions (black and white bars) and during winter-like (black and grey bars) and winter-like + light exposure (yellow bar). Right: Amplitude of locomotor activity rhythms at different experimental conditions. **d** Daily average onsets (hours before lights on) and offsets (hours after lights off) of activity showing a phase-advance under winter-like photoperiodic conditions in comparison to the LD12/12h control condition. Light exposure at ZT7 delays significantly activity onsets and offsets of locomotor activity rhythms. Data are shown as the mean ± SEM. Means lacking common letters are significantly different (between groups LSD post hoc test, $p < 0.05$)

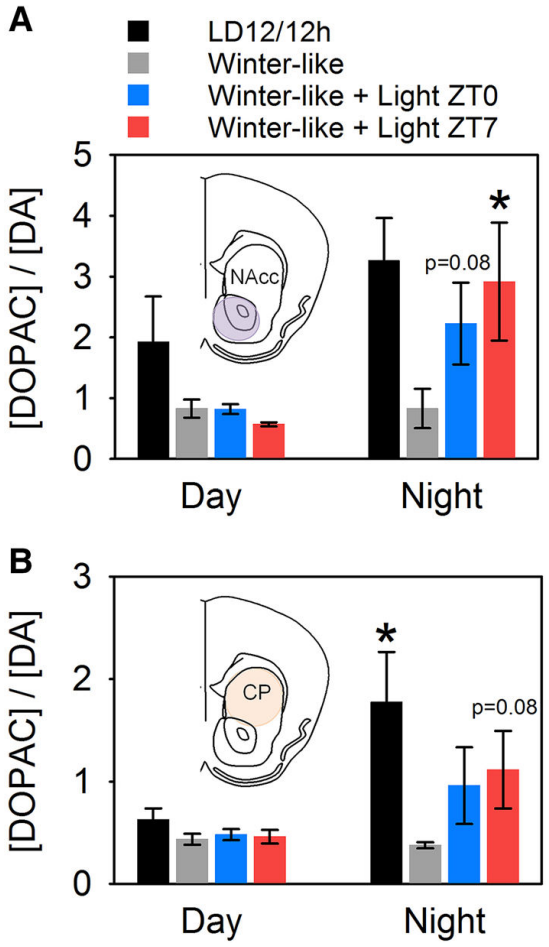

Fig. 3 Effects of winter-like photoperiod and light exposure on brain dopamine (DA). DA turnover (ratio of metabolite 3,4-dihydroxyphenylacetic acid DOPAC/DA) in brain tissue samples of nucleus accumbens (NAcc) (**a**) and dorsal striatum (caudate–putamen, CP) (**b**). Samples were obtained at day (Zeitgeber Time, ZT7) and night (ZT19). There is a loss of the day–night variations of DA turnover when animals are exposed to winter-like photoperiods compared to control LD12/12h conditions in both NAcc and CP. Light exposure at early day (ZT0) or late day (ZT7) increase DA turnover at night rescuing rhythmic brain DA in the NAcc although at ZT0 the *p* value was not significant ($p = 0.08$). In the CP, there was also a tendency to increase DA turnover at night by light, but the post hoc analyses were not significant ($p = 0.08$). Data are shown as the mean ± SEM. *$p < 0.05$ (ZT7 vs. ZT19) (LSD Fisher post hoc comparison)

Table 1 Day–night (ZT7 vs. ZT19) dopaminergic changes in the dorsal striatum (CP) and nucleus accumbens (NAcc) of animals under control (LD12/12h), winter-like (LD8/16h) and winter-like + light conditions, with light exposure at ZT0 (early day) or ZT7 (late day)

	Control (LD12/12h)	Winter-like (LD8/16h)	Winter-like + Light (ZT0)	Winter-like + Light (ZT7)
	Day/night	Day/night	Day/night	Day/night
NAcc				
Dopamine *(pg/mg)*	17.8±4.9[a]	67.6±14[b]	36.5±6.8[a]	76.2±6.9[b]
	10.7±1.9[a]	99.6±39.1[b]	15.9±3.8[a]	27.6±9.1[a]*
DOPAC (pg/mg)	26±3.6[a]	52.1±2.4[a]	27.9±5.3[a]	43.7±5[a]
	33.6±9.8[a]	57.7±8.8[b]	28.4±7.8[a]	46.1±7.8[b]
CP				
Dopamine *(pg/mg)*	59.3±12[a]	112.3±11.6[a]	66.2±12.5[a]	93.3±16[a]
	20.9±3.5[a]	190.5±42.5[b]	38.8±15.6[a]	73.2±46.2[a]
DOPAC (pg/mg)	37.4±11.6[a]	48.8±7.1[a]	29.9±4.7[a]	40.1±5.2[a]
	35.9±8.8[a]	71.3±15[b]	30.3±11.4[a]	37.6±8.1[a]

Values represent the mean values ± SEM.

Means lacking common letters are significantly different (between groups post hoc test, $p < 0.05$).

* $p < 0.05$, between ZT's

Daily light exposure effects on clock gene expression in the SCN of winter-like exposed animals

Day–night expression of *Per2*, but not *Bmal1*, gene in the SCN was down regulated by winter-light condition in comparison to LD12/12h conditions (Fig. 4a, b, $F_{(3,29)} = 4.2$; $p = 0.017$). Day–night expression of *Avp*, a clock output gene, in the SCN was not affected in winter-like animals in comparison to control LD12/12h *Arvicanthis* (Fig. 4a, b, $F_{(3,28)} = 0.69$; $p = 0.56$).

Then, we analyzed the effects of 1 h daily bright light exposure at the early (ZT0) or late day (ZT7) on clock gene expression in the SCN of animals exposed to winter-like photoperiods. Day–night expression of the *Per2* gene in the SCN, down regulated in winter-light exposed animals, was not significantly affected by light exposure at ZT0 or ZT7 ($F_{(3,29)} = 0.98$; $p = 0.41$) despite an increase of expression at daytime (ZT7, Fig. 4a, b). However, the ANOVA indicated a significant difference in the interaction of housing conditions (LD12/12h vs. winter-like vs. winter-like + light) and time factors (day vs. night), in which the expression of *Per2* in the SCN at day was different between LD12/12h control animals, winter-like and winter-like + light exposed animals at ZT0, but not at ZT7 (Fig. 4b, $F_{(3,29)} = 4.2$; $p = 0.017$). This effect might suggest a mild but significant rescue of *Per2* expression by light exposure at ZT7 in winter-like exposed animals. Finally, the *Bmal1* and *Avp* day–night expression in the SCN was not affected by light exposure at ZT0 or ZT7 in winter-like exposed *Arvicanthis* (Fig. 4a, b; *Bmal1,* $F_{(3,27)} = 0.29$; $p = 0.82$; *Avp,* $F_{(3,28)} = 0.69$; $p = 0.56$).

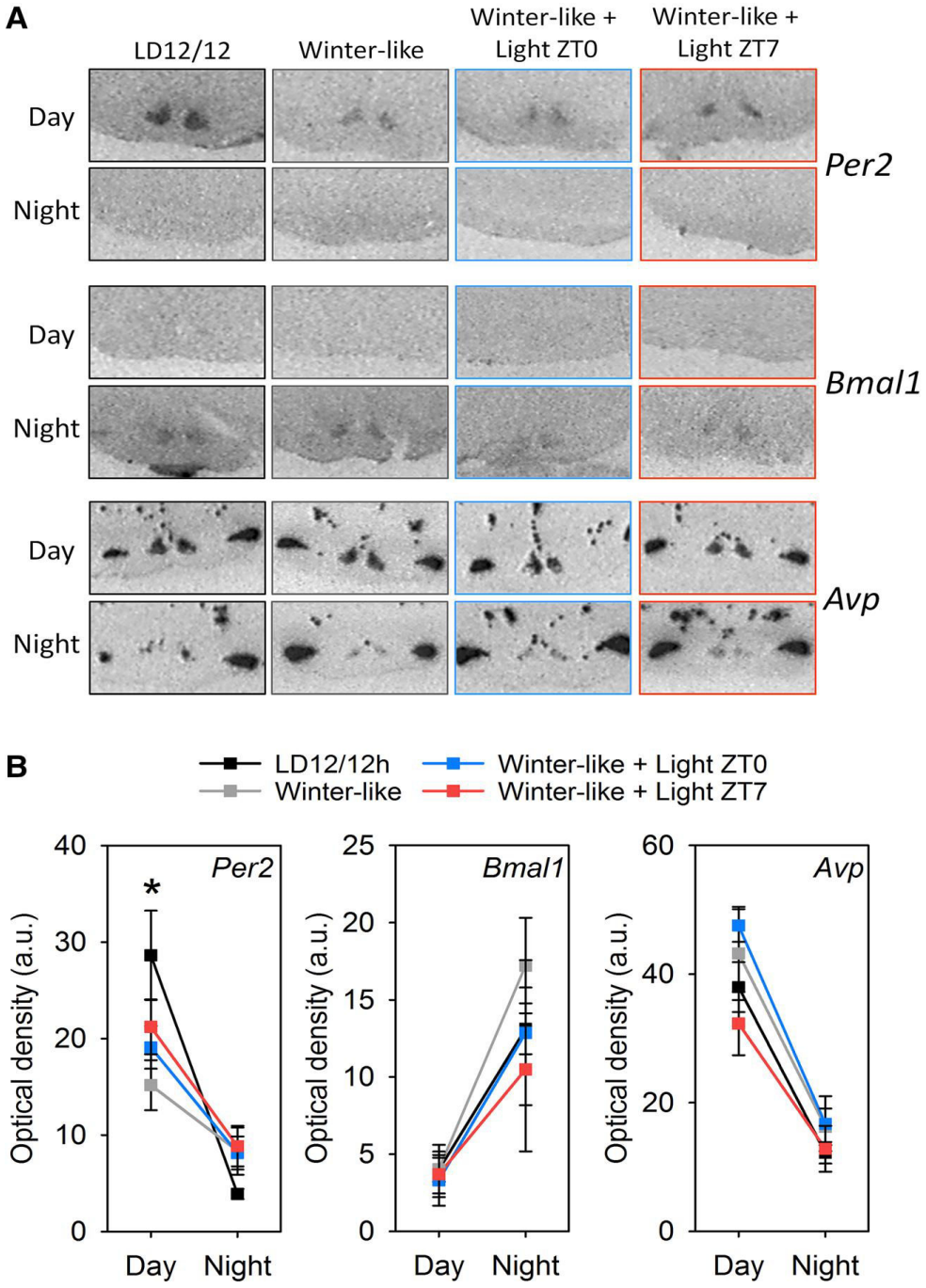

Fig. 4 Daily light effects on the day–night expression of clock genes in the SCN of winter-like exposed animals. **a** Representative images of in situ hybridization and **b** day–night expression of *Per2, Bmal1* and *Avp* in the SCN of *Arvicanthis* under different experimental conditions. Data are means ± SEM. *$p < 0.05$ LSD Fisher post hoc comparison; *Per2* expression at ZT7 from LD12/12h group is significantly different to the winter-like and winter-like + light ZT0 group

Discussion

In the present study, we observed that when diurnal rodents *Arvicanthis ansorgei* are exposed to a winter-like photoperiod, consisting of a LD8/16h cycle with low light levels (45 lux) during the day, animals show altered synchronization to the LD cycle, day–night brain DA content and clock gene expression in the SCN. Importantly, these effects in circadian behavior, DA content and SCN *Per2* gene expression were reverted when animals were treated with a daily light exposure late in the day. However, when light exposure was applied at the early day DA changes, but not the daily rhythm of locomotion, were rescued. These results indicate that daily light exposure can rescue altered behavior and physiology induced by a winter-like photoperiod in a time-dependent manner.

In depression, the daily activity rhythm is often disturbed (Raoux et al. 1994; Volkers et al. 2002). Moreover, the amount of activity is reduced in depressed patients, including those suffering from SAD (Raoux et al. 1994; Teicher et al. 1997). The phase shift hypothesis in SAD accounts, patients show rest-activity cycles and other physiological rhythms (e.g., body temperature, melatonin) that are phase delayed (Dahl et al. 1993; Teicher et al. 1997; Terman et al. 1988). Here we observed that *Arvicanthis ansorgei* shows shifted locomotor activity rhythms when exposed to a winter-like photoperiod, but the phase shift found was an advance rather than a delay. This suggests that winter-like photoperiod affects circadian rhythms of behavior by producing phase shifts that are not stringent upon direction (advance or delay). Previously, other diurnal rodents showed similar changes in the phase angle of entrainment, desperate behavior (evaluated by FST) and sucrose consumption when exposed to short photoperiods (Ashkenazy-Frolinger et al. 2010; Deats et al. 2015; Krivisky et al. 2011; Leach et al. 2013b, a). Importantly, in one study, *Arvichantis niloticus* showed reduced saccharine preference and desperate behavior in the FST solely when exposed to dimmer day light intensity (50 lux) despite unchanged day length (LD12/12h) (Leach et al. 2013a). SAD patients tend to exhibit hypersomnia, weight gain, increased appetite and evening carbohydrate craving (Berman et al. 1993; Lewy et al. 2006). Sucrose intake in *Arvicanthis ansorgei* increases when animals are exposed to the winter-like photoperiod (data not shown) in agreement with eating attitudes in SAD patients.

Other central clinical features of SAD are low mood, lack of drive and concentration, and decreased interest, with reduced activity levels, which leads to attenuation of the amplitude of the daily rhythm of activity (Lam and Levitan 2000). Whereas desperate behavior observed in previous studies using diurnal rodents clearly indicates the effects of photoperiod conditions in mood (Ashkenazy-Frolinger et al. 2010; Krivisky et al. 2011), more studies using other behavioral tests or models are still necessary.

Alterations of clock gene expression have been implicated in the appearance of psychiatric pathologies including depression (Albrecht 2017). In humans, seasonal (winter) depression has been associated with the clock genes *Per2, Bmal1* and *Npas2* (Partonen et al. 2007). Here, we found that day–night expression of *Per2*, but not *Bmal1*, in the SCN is affected in *Arvicanthis* exposed to winter-like conditions. In mice showing depressive-like behaviors *Per2* expression is also decreased in the SCN (Logan et al. 2015). Nevertheless, *Per2* mutant mice are resistant to depressive-like behavior (evaluated in the FST) due to higher brain DA release (Hampp et al. 2008). However, because in *Arvicanthis* exposed to winter-like conditions there was a significant phase-advance of daily rhythms, it is possible that the down regulation at daytime is the consequence of a phase shift rather that an inhibitory effect of photoperiod on *Per2* gene expression. Indeed, in mice with depressive-like

behavior the daily rhythm of *Per2* expression in the NAcc and SCN is phase shifted (Logan et al. 2015). It will be interesting to evaluate the daily profile of *Per2* gene expression in the SCN of winter-like exposed *Arvicanthis*.

The monoaminergic hypothesis has implicated various neurotransmitter systems in the pathophysiology of depression, including the serotonergic system (5-HT) (Russo and Nestler 2013; Neumeister et al. 2001). Brain 5-HT concentrations and activity of the serotonin transporter (5-HTT) vary with seasons; In addition, 5-HTT turnover rate is affected in the forebrain of SAD patients (Willeit et al. 2008). These results are in line with findings in diurnal rodents on the effect of short photoperiods in 5-HT neurons in the raphe nuclei (Leach et al. 2013b). Moreover, Selective Serotonin Reuptake Inhibitors (SSRIs) have been used as first-line therapy for depression. One SSRI, escitalopram, has been found to suppress the mean firing rate of VTA DA neurons through enhanced activation of 5-HT2C receptors likely on GABA neurons (Dremencov et al. 2009). This finding, with data on catecholamine changes in patients treated with bright light, yields new insight into the role of DA in SAD (Cawley et al. 2013). Here, we examined the DAergic content and turnover in two forebrain reward system structures, the CP and NAcc, in *Arvicanthis ansorgei* exposed to winter-like photoperiods. DAergic afferents to both areas arise from the midbrain VTA to modulate motor coordination, reward, motivation and emotion-related behaviors (Berridge and Kringelbach 2013). These and other reward system structures possess circadian activity in several forms (Mendoza and Challet 2014). Here, higher DA turnover (DOPAC/DA ratio) was found at night (ZT19) than day, a day–night difference that was blunted in winter-like conditions. Since the DOPAC/DA ratio reflects DA activity, the reduction of this ratio in winter-like animals indicates a decrease in DA metabolism. However, due to the rhythmic activity of DAergic system (Mendoza and Challet 2014), it is possible that the reduced levels of the DOPAC/DA ratio in animals exposed to winter-like conditions reflect a phase change of DA turnover induced by the photoperiodic conditions. Further experiments using in vivo microdialysis to measure DA release could give important information about the effects of winter-like conditions in DAergic activity in *Arvicanthis ansorgei*.

Similarly, in *Arvicanthis niloticus*, the number of hypothalamic DA neurons of animals housed in short photoperiod is downregulated (Deats et al. 2015). Long-term light deprivation in rats has been found to damage the monoaminergic system, including DA, 5-HT and noradrenaline (NA), and induce depression-like behavior (Gonzalez and Aston-Jones 2008). All together, these findings suggest the DA system can be affected by changes in the daytime length and light intensity (Abilio et al. 1999). In accordance with animal data, several studies reported changes in the DAergic activity secondary to SAD or even due to seasons in healthy people (Eisenberg et al. 2010; Hartikainen et al. 1991). All together, these studies indicate that lighting conditions affect the DAergic system.

Biological timing is strongly affected in SAD and light is the most powerful synchronizer of the biological clock in the SCN, suggesting why light therapy has become as one of the most prolific treatments for SAD. The beneficial effect of bright light in SAD has been observed in the phase and levels of locomotor activity and physiology in patients (Burgess et al. 2004; LeGates et al. 2014; Wirz-Justice et al. 1993). Daily light exposure in *Arvicanthis*, either at the early day (ZT0) or late day (ZT7), has a tendency to reduce sucrose intake (data not shown), holding up the predictive validity of light effects in behavior. To note, light has been proposed to treat night eating disorders in which people reduce food intake at night, mood and sleep disturbances when treated with bright light (McCune and Lundgren 2015). However, the present study, the efficacy of light to delay the onset of

locomotor activity and to restore the phase of the behavioral rhythm was significant only in animals exposed to light at the late day (ZT7).

In humans, light therapy is imposed mainly at the early morning (Lewy et al. 2006). The phase response curve (PRC) to light in humans using a single light pulse, and using the midpoint of the melatonin rhythm as a phase marker, indicates that light causes phase delays when it occurs in the late night, and phase advances in the early morning (St Hilaire et al. 2012; Ruger et al. 2013). In SAD, light at the early morning is the recommended treatment since its antidepressant effects correct the delayed phase of circadian rhythms caused by winter conditions (Lewy et al. 1998).

In *Arvicanthis ansorgei* phase delays occur when light exposure is applied at the beginning of the night, whereas light exposure at the early day leads in phase advances of behavioral rhythms (Caldelas et al. 2003). Thus, in the present study, the phase-advanced behavioral rhythm in *Arvicanthis* under a winter-like condition is delayed when daily light occurred at the late, but not early day. Moreover, day–night *Per2* gene expression in the SCN was affected in animals exposed to light at ZT7. *Per2* expression in the SCN of *Arvicanthis ansorgei* rises at daytime in animals exposed to a 12/12 LD cycle (Caldelas et al. 2003). Moreover, light exposure at the early subjective night induces *Per2* expression in the SCN of *Arvicanthis* (Caldelas et al. 2003). Here, in *Arvicanthis* exposed to 1 h light pulses at ZT7 induced a slight, but significant, rescue of the day–night expression of *Per2* in the SCN of *Arvicanthis* under winter-like conditions accompanying the resetting (phase delays) of the rhythm of locomotor activity. Interestingly, in humans, phase is not relevant for the beneficial effects of light in mood (Wirz-Justice et al. 1993). Hence, even if light at the early morning (ZT0) does not restore the phase of locomotor activity in *Arvicanthis*, mood-related behavior could be affected by light independently of the time of exposure. This suggests that rhythm alterations (phase change or amplitude) induced by winter-like exposure might not be totally part of the pathology in SAD. In *Arvicanthis*, the exposure to daily light at ZT0 induces an increase of locomotor activity. Physical activity has reward and antidepressant properties affecting the DAergic system (Brene et al. 2007). Therefore, despite no effects in phase resetting by light at ZT0, the improved DA tone in animals might dependent on the locomotor activity induced by light. Importantly, it has been reported that both light and physical activity in the day reduce depressive symptoms in patients with winter depression and non-seasonal depression (Pinchasov et al. 2000). Together, these features make *Arvicanthis* an adequate diurnal animal model to study the light impact in physiology and behavior, circumventing the light aversion found in traditional nocturnal rodent models. Despite its efficacy, the neural mechanism by which light ameliorates mood remains to be clarified.

Light, beyond the SCN clock, also targets other brain structures implicated in mood and depression. For instance, the effects of light exposure on DAergic structures have been shown both in humans (Diehl et al. 1994) and animals (Abilio et al. 1999). Moreover, an experiment in which DA synthesis was reduced in women with mild seasonal mood changes and reversed with bright light therapy, suggested that DA changes induced by light may be partly necessary for the beneficial effects of light in mood (Cawley et al. 2013).

In the present experiments, daily light exposure resolved DA turnover disturbances elicited by winter-like conditions as expected; it increased the DOPAC/DA ratio in the NAcc and CP which suggests an increased DA metabolism and release. DA tone is implicated in a variety of circadian rhythms such as feeding, sleep-wake, locomotion and motivation, which are disrupted in SAD (Lam

and Levitan 2000; Lewy et al. 2006). Thus, light effects on mood might be dependent on regulating mechanisms on the DA activity (Neumeister et al. 2001).

Current models of mood regulation by light account for two main pathways, an indirect one mediated by circadian rhythms and a direct route that does not disrupt sleep or cause circadian changes (LeGates et al. 2014). The circadian clock is connected to the reward system via several circuits, e.g., the SCN is connected to the VTA via the medial preoptic nucleus of the hypothalamus or the lateral hypothalamic orexinergic system, and to the striatum via the paraventricular thalamic nuclei (Luo and Aston-Jones 2009; Moga et al. 1995; Moorman and Aston-Jones 2010). And very recently, a study demonstrated the existence of a direct functional projection from the DAergic VTA to the SCN clock (Grippo et al. 2017). A previous work revealed that light exposure in early subjective day increases c-Fos expression in orexin neurons in *Arvicanthis niloticus* (Adidharma et al. 2012), suggesting a role of orexin in mediating the effects of light on mood. In the same study, however, c-Fos expression in the SCN was not induced by light exposure, indicating light modulation by SCN-independent pathways.

The lateral habenula (LHb) in the mid-posterior thalamus could account for direct effects of light on mood (Lazzerini Ospri et al. 2017). It receives projections from retinal ganglion cells and is involved in reward processing for relevant control of monoaminergic system in the VTA (for DA) and raphe nuclei (for 5-HT) (Hattar et al. 2006; Baker and Mizumori 2017). Moreover, the LHb possess oscillating properties which coordinate with the SCN to control circadian rest/activity rhythms (Mendoza 2017; Salaberry and Mendoza 2015), and short brief light pulses at the early night in *Arvicanthis niloticus*, but not in mice, increase c-Fos expression in the LHb (Shuboni et al. 2015). As intermediary structures it is necessary to elucidate the respective contribution of the direct or indirect pathway of the modulation of mood by light. Nonetheless, this diurnal animal model might provide adequate means to elucidate this matter.

In conclusion, this study has brought light to the potential of the diurnal *Arvicanthis ansorgei* to reveal the effects of light in behavior and brain physiology (i.e., DAergic system).

Several questions, regarding particular manifestations of SAD and its treatment by light, demand further probing. Their elucidation will overflow into the understanding of the neurobiological and circadian mechanisms of light effects in behavior (e.g., mood, eating disorders).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving animals were in accordance with the Guide for the Care and Use of Laboratory Animals (NIH Pub. No. 86-23, revised 1985) and the French Department of Agriculture (License no. 67-378 to J.M.).

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Chapter 3: Environmental light and time of day modulate subjective liking and wanting

Environmental light and time of day modulate subjective liking and wanting

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Abstract

Clinical and laboratory studies demonstrated effects of light on affect. Few field studies investigated how naturally fluctuating light levels affect positive and negative mood in everyday life, but none addressed two key components of the reward system: wanting and liking. To elucidate diurnal profiles as well as immediate effects of dynamically changing light intensity in everyday life, subjective wanting and liking were assessed using experience sampling, while continuously monitoring environmental illuminance. Using a smartphone and light sensors, healthy volunteers (n=27, 14 females, 23.7 ± 3.8 (M ± SD) years of age) were probed for one week, nine times a day, to rate positive and negative mood, and six novel dedicated questions each on subjective liking and wanting. The multiband light spectrum was continuously recorded from sensors worn on the chest and intensities were averaged over the intervals between subsequent probes. Mixed effect models were used to evaluate how time of day and light intensity modulated subjective ratings. A total of 1102 valid time points indicated that Liking and Wanting peaked around 6PM and increased, respectively, by 13 ± 4% and 11 ± 4% across an individual's range of experienced light intensities. More traditional mood questions showed less sensitive to modulation by light intensity. Naturally occurring fluctuations in environmental light affect wanting and liking. Combined experience sampling and environmental monitoring opens the possibility for field studies on light in disorders in which the reward system is highly relevant, like addiction, depression, insomnia and obesity.

Introduction

Environmental light has a strong effect on several behavioral and physiological functions including the regulation of sleep, circadian rhythms, body temperature and mood - the topic of the present study. Several studies demonstrate that mood varies across seasons, possibly in association with changes in the duration of daylight. The most telling example of such mood modulation is seasonal affective disorder. A few weeks of daily bright light therapy can alleviate the depressive symptoms. Well controlled studies reported effects of prolonged periods of daily light exposure on mood (Eastman et al., 1998; Lieverse et al., 2011; Riemersma-van der Lek et al., 2008; Terman et al., 1998; Wirz-Justice et al., 2004). Mood disorders involve major disturbances on the brain reward system (Russo and Nestler, 2014). Indeed, activation of the reward circuitry changes with light intensity (LeGates et al., 2015; Vandewalle et al., 2011, 2010).

Traditionally, non-image forming effects of light on the reward system were considered to be mediated by circadian clock in the hypothalamic suprachiasmatic nucleus (SCN). The SCN receives dense projections from the intrinsically photosensitive Retinal Ganglion Cells (ipRGCs) (Hattar et al., 2002). These ipRGCs have the capacity to integrate retinal information on environmental light intensity and transmit this information to the SCN (Berson et al., 2002). In turn, projections from the SCN to reward brain structures (e.g. ventral tegmental area, lateral hypothalamus) provide a pathway that could mediate effects of light on the reward system (Mendoza and Challet, 2014). A more direct pathway has emerged as well during the last decades: ipRGCs have functionally relevant direct projections to limbic areas involved in the regulation of mood and reward, including the lateral habenula, medial amygdala, and periaqueductal grey (Hattar et al., 2006, 2002; LeGates et al., 2012; Ren et al., 2014).

Studies on the effect of light intensity on the reward system in humans have mostly been confined to the evaluation of mood ratings. Several laboratory studies demonstrated acute effects of environmental light intensity on the evaluation of affect elicited by stimuli (Revell et al., 2006; Vandewalle et al., 2011, 2010). The light intensity of the stimuli itself has an effect on affect evaluations as well: brighter versions of neutral pictures are evaluated more positively than darker versions of the same picture (Lakens et al., 2013). Only few studies addressed the effect of light intensity on mood ratings in naturalistic environments (aan het Rot et al., 2008; Dumont and Beaulieu, 2007). In a study on social interactions in people with mild seasonal mood complaints, high intensity light exposure improved mood, reduced quarrelsome behaviors, and promoted more agreeable behaviors (aan het Rot et al., 2008). Field studies have however insufficiently addressed the effect of light exposure on two major discriminable components of reward processes: liking and wanting (K. C. Berridge & Robinson, 2003; Kringelbach & Berridge, 2009). Liking refers to the pleasure component of a reward. Wanting represents the incentive motivation that promotes approach toward and consumption of rewarding stimuli. Liking can be subjectively experienced as feelings of pleasure or niceness, and wanting as desires for incentives or declarative goals. With respect to their representation in the brain, wanting and liking involve partially distinguishable brain circuits. Liking and wanting have been studied in the context of anhedonia, reward circuitry dysfunctions like depression, eating disorders and addiction (Born et al., 2011; Robinson, Fischer, Ahuja, Lesser, & Maniates, 2016; Rømer Thomsen, Whybrow, & Kringelbach, 2015; Treadway & Zald, 2011). However, field studies on the immediate effect of dynamically changing light levels on these components of the reward system have not been published so far.

To broaden insight in the effects of light exposure on these key concepts of the reward system, the present field study combined ambulatory assessment using wearable sensors with the method of Experience Sampling (ES) to assess how naturalistic fluctuations in environmental light level affect subjective liking and wanting. Compared to traditional retrospective self-reports ES diminishes recall bias and selectivity by capturing current or recent behaviors. Furthermore, ecological validity is high compared to lab studies because subjective experiences can be described as they occur in the naturalistic environment (Reis, 2012). Given their fundamental role in the regulation of reward processes, we evaluated subjective wanting and liking next to more traditional mood ratings.

Methods

Participants

Volunteers (13 males, 14 females, M age = 23.7 ± 3.8 years, age range = 18-33 years) were recruited by advertisement and word of mouth. An online screening form verified the eligibility of candidates to participate in the study. All participants provided written informed consent. Inclusion criteria were an age between 18 and 40 years, self-acclaimed good health and working regular office hours. Exclusion criteria were ocular pathology, drug abuse, excessive alcohol consumption (>10 glasses per week), use of alertness, sleep and thermoregulation-altering medication and any current somatic, psychiatric or neurological disorder. Participants received monetary compensation after study completion. The protocol was approved by the Ethics Committee of the VU University and Medical Center and performed in accordance with principles of the Helsinki Declaration.

Procedure

Volunteers participated in unconstrained ambulatory assessment in their natural environment for seven consecutive days. On the day prior to the start of the ambulatory assessment, subjects were introduced to the project, familiarized with the usage of a smartphone for Experience Sampling (ES) and attachment of the light sensors to their clothes.

Light Assessment

Participants received two dime-sized RGB multiband light sensors (Dimesimeter, also known as Daysimeter-D, Rensselaer Polytechnic Institute, Troy, NY, USA) (Bierman et al., 2005; Figueiro et al., 2013). Photopic illuminance and the multiband light spectrum were sampled once every minute from the moment they woke up until bedtime for seven consecutive days. Each participant received two brooches with an integrated sensor. One of the brooches was pinned at chest level on the indoor clothing a participant chose to wear on each particular day from the moment they woke up until bedtime. The other brooch was pinned on the participant's outdoor jacket or coat at the same chest level and left there for all days this jacket or coat was used. The use of two brooches allows for continuous indoor and outdoor assessment: when the brooch on indoor clothing is covered by one's coat or jacket, the signal recorded from the brooch on the coat or jacket can be used to estimate environmental light level. Whether a coat is worn, could be assessed from the accelerometry signal integrated in each sensor.

Assessment of Liking and Wanting

Experience Sampling (also known as ecological momentary assessment) was used to repeatedly assess momentary subjective liking and wanting. The method was implemented using MovisensXS software (Movisens GmbH, Karlsruhe, Germany) installed on a smartphone (Nexus 4, LG, Seoul,

Korea). Participants were probed 8 times a day at quasirandom intervals (ranging from 16 minutes to 3 hours) timed between 8:00 and 22:00 hr, and were asked in addition to provide input after waking up and before bedtime. Preceding the first observation of each day, which was made immediately upon awakening, the subjects were asleep with eyes closed, usually in a dark bedroom. Hence the first observation of the day lacks variance in prior light exposure and was therefore not considered in the present study. The assessment of explicit and implicit liking and wanting in humans is an area that is under development (Born et al., 2011; Finlayson, King, & Blundell, 2007; Parsons, Young, Kumari, Stein, & Kringelbach, 2011; Tibboel, De Houwer, & Van Bockstaele, 2015). Only after we commenced data collection, other work on ES related to these domains appeared (Depp et al., 2016; Hofmann, Adriaanse, Vohs, & Baumeister, 2014), . In the absence of existing methods, EVS and MK generated items for a comprehensive assessment of the domains of liking and wanting. Items were phrased in such a way that it would fit the limited space on a smartphone screen. Subjective liking and wanting were surveyed at every prompt by six statements each, addressing the dimensions of "taste-smell", "bodily sensation", "watching/listening", "social interaction", "physical activity" and "receiving something". Participants were asked to rate the extent to which each statement applied to them in the period between the current and previous alarm, using visual analogue scales (VAS) with end points not and very much scaled to 0 and 100 respectively. The statements are shown below: liking (in Dutch: "genoot ik van…") was queried first and immediately followed by questions on wanting (in Dutch: "had ik zin in…").

Since the previous alarm, I enjoyed...

	not	very much
... a taste or smell	|----------	----------|
... a bodily sensation	|----------	----------|
... watching or listening	|----------	----------|
... interactions with other	|----------	----------|
... physical activity, being busy	|----------	----------|
... receiving something	|----------	----------|

Since the previous alarm, I wanted...

	not	very much
... a taste or smell	|----------	----------|
... a bodily sensation	|----------	----------|
... to watch or listen	|----------	----------|
... to interact with others	|----------	----------|
... physical activity, to be busy	|----------	----------|
... to receive something	|----------	----------|

Assessment of Previously Used Mood Adjectives

In contrast to the prior lack of ES-items addressing liking and wanting items, several studies reported positive and negative mood adjectives. To evaluate whether these adjectives are differentially sensitive to the effects of light intensity as the new direct questions on wanting and liking, we also included the positive and negative mood adjectives of the Daytime Insomnia Symptom Scale (DISS) (Buysse et al., 2007). Positive Mood was assessed using the five DISS items 'Relaxed',

'Energetic', 'Calm', 'Happy' and 'Efficient'. Negative mood was assessed using the five DISS items 'Anxious', 'Stressed', 'Tense', 'Sad', and 'Irritable'.

Preprocessing

Light

Dimesimeter measurements were preprocessed with MATLAB 2014a (MathWorks Inc., Natick, Massachusetts, USA). One Dimesimeter was worn on the indoor clothing and one on the outdoor clothing. The accelerometry and photopic illuminance signals of the two Dimesimeters were synchronized by means of the recorded timestamps and used to assess the validity of each light sample. The accelerometry signal was used to assess if none, one or both of the devices were worn. The photopic illuminance signal was used to assess if the sensor was covered (e.g. by clothing). Visual inspection of the accelerometry signals indicated baseline noise in the absence of movements. Values below the baseline noise floor were set to zero. Windows of at least 15-minutes without activity were marked as periods that the sensor was not worn and excluded from analyses. This interval was based on a previous study that demonstrated the virtual absence of periods of immobility lasting more than 15 minutes during normal wakefulness (Romeijn et al., 2012). Epochs during which no single photopic illuminance value was larger than zero were excluded from analysis as well, because they indicate that the sensor was covered. The remaining one-minute epochs were considered valid measurements.

For each valid epoch the light value of either the indoor or the outdoor clothing device was selected. If only one of the sensors had a valid measurement, the light measurement of the valid measurement was selected. If both sensors simultaneously showed valid measurements, the sensor with the maximal photopic illuminance measurement was selected. If none of the two devices had valid measurements, the sample was discarded. The photopic illuminance and accelerometry signals were used only to assess which device to choose. All subsequent analyses utilize the co-recorded multiband spectrum. The co-recorded multiband spectrum value of each valid photopic illuminance sample was nonlinearly transformed into a value between zero and one that represents the estimated downstream effect of the light intensity on the circadian system, as derived from its effectiveness to suppress melatonin (circadian stimulus, CS (Rea, Figueiro, Bierman, & Bullough, 2010)), hereinafter referred to as 'light intensity'. CS-transformed light intensity values were averaged within each time interval between subsequent alarms. Intervals exceeding three hours were discarded. The resulting set of averaged CS-transformed light intensity values was used for mixed effect regression analyses.

The CS transformation of multiband spectra linearized the nonlinearly distributed wide range of illuminance values. For visualization purposes only, the range of interval CStransformed light intensity averages within each participant were assigned to ten deciles, and averaged across participants within each decile. The upper panel of Figure 1 shows the highly nonlinear decile distribution of photopic illuminance averages, whereas the middle panel shows the linearized decile distribution of CS-transformed interval light intensity averages.

Liking, Wanting and Positive and Negative Mood Adjectives

For each interval, a Liking and Wanting score was calculated by averaging the six VAS ratings in each of the domains assessed by experience sampling at the end of the interval. Likewise, for each interval, Positive Mood and Negative Mood scores were calculated by averaging the five DISS items of each domain. Intervals with incomplete or ignored experience sampling assessments were discarded.

Statistical Analysis

Mixed-effect regression models were used to evaluate how Liking and Wanting changed with time of day and light intensity. Time of day was included in the models because diurnal rhythms have been demonstrated in reward behavior and neurophysiology (Webb, Lehman, & Coolen, 2015) and subjective hedonic tone (Jankowski & Ciarkowska, 2008). Time-of-day effects were estimated using the equivalent linear form of a 24-hour cosine curve (Fernández and Hermida, 1998) that combined the sine and the cosine of the time of each interval, defined as the mid time between the current and previous alarm, expressed in radians of a 24 hr (2π) cycle where 0 and 2π represent midnight.

In order to be able to discriminate within-subject effects from between-subject effects of light intensity on subjective Liking and Wanting, an average CS value was calculated for each individual, which was included in the model next to the within-subject-centered residual fluctuation around his or her average (van de Pol and Wright, 2009).

The 3-level hierarchical structure of variables measured during variably timed intervals (i), nested within days (j), nested within subjects (k) was accounted for by using random effects for subjects and days nested within subjects to control for the influence of different mean ratings associated with these variables (i.e. random intercepts). All analyses started with a null model that included the dependent variable and the subjects and days within subjects as random factors. Independent variables were added incrementally to see if the model improved.

Mixed-effects models were estimated using the 'lme4' package (Bates, 2015) for R version 3.2.4 (R Core Team, 2016). Summary statistics and 95% confidence intervals (CIs) were calculated using a bootstrap procedure of 10000 replications (Davison & Hinkley, 1997) using the 'boot' package (Canty & Ripley, 2016). P values for regression coefficients were obtained by calculating the fraction of 10000 bootstrapped LRT-values that are larger or equal to the observed LRT value obtained from comparing the model with and without the independent variable.

Initially fitted models on the effect of time of day and light intensity on subjective Liking, Wanting, Positive mood and Negative mood measured over interval i of day j of participant k were as follows:

$$
\begin{aligned}
Y_{ijk} = {} & \beta_{0jk} \\
& + \beta_1 * \mathrm{SineTimeOfDay}_{ijk} \\
& + \beta_2 * \mathrm{CosineTimeOfDay}_{ijk} \\
& + \beta_3 * \mathrm{LightIntensitySubjectCentered}_{ijk} \\
& + \beta_4 * \mathrm{LightIntensitySubjectAverage}_{k}
\end{aligned}
$$

Where Y is the dependent variable, either Liking, Wanting, Positive mood or Negative mood

$ß_0$ is the intercept allowing for random variation over days *j* and participants *k*, $ß_1$ and $ß_2$are the sine and cosine components of the linear form of a 24-hour cosine curve to capture diurnal variation and

$ß_3$ and $ß_4$ are the effects of the within-subject-centered fluctuations, and average between-subject differences, in light exposure. Note that the non-significant subject-averaged light intensity term was omitted from the final reported models.

The fitted model for the modulation of light intensity by time of day measured over interval i of day j of participant k was as follows:

$$LightIntensity_{ijk} = ß_{0jk} + ß_1 * SineTimeOfDay_{ijk} + ß_2 * CosineTimeOfDay_{ij}$$

Where $LightIntensity_{ijk}$ is the dependent variable

$ß_0$ is the intercept allowing for random variation over days *j* and participants *k*

ß1 and *ß2* are the sine and cosine components of the linear form of a 24-hour cosine curve to capture diurnal variation.

Results

Data were collected for a total of 1701 time points. Incomplete surveys, dismissed or ignored by the participant, were discarded (8.8%). Moreover, we discarded all surveys for which the interval to the previously completed survey was longer than 3 hrs, i.e. the maximal interval between the generated alarms (6.1%), and intervals without valid light measurements (18.3%). Two participants had less than 10 valid observations and were excluded from all analyses because of probable compliance issues or technical failures (0.7%). After fitting the models, outlying data points identified by evaluating the model residuals and discarded from the final refitted models (Baayen, 2008). Outlying data points were those of which the standardized residuals exceeded 2.5 times the standard deviation of the residuals (1.2%). The remaining 1102 observations were included in the analyses.

Across all observations of all participants, Wanting ranged from 0 to 96 and Liking from 0 to 95 out of a possible range of 0-100. Individual response ranges for Wanting and Liking spanned from 20 to 64 and from 26 to 79 VAS points respectively. Across all observations CS ranged from 0 to 0.74 out of a possible range of 0-1. Individual light intensity exposure spanned ranges from 0.33 to 0.72 units of CS.

Modulation of Light Exposure by Time of Day

Time of day significantly modulated light intensity, which peaked at 13:35 hr (Sine component: -0.07 ± 0.01 [-0.09, -0.05] (effect estimate ± standard error on the estimate, [95% confidence interval]), p = .0001; Cosine component: -0.16 ± 0.01 [-0.17, -0.14], p = .0001; Figure 1).

Modulation of Wanting and Liking by Time of Day and Light Exposure

Time of day significantly modulated Wanting, which peaked at 17:49 hr (Sine component: p = .0001; Cosine component: p = .83, Table 1), and Liking, which peaked at 18:50 hr (Sine component: p = .0001; Cosine component: p = .20). Within-subject variability in light intensity significantly affected Wanting (p = .0013) and Liking (p = .0001). Between-subject differences in average light exposure intensity did relate to their average Wanting or Liking (p = .38, p = .32, respectively).

Across the range of an individual's lowest to highest light exposure values, Wanting and Liking were estimated to increase, respectively by 11 ± 4% (4-21) (mean ± standard deviation (range)) and 13 ± 4% (6-25) of the within-subject observed range in their ratings.

Modulation of Positive and Negative Mood by Time of Day and Light Exposure

Time of day significantly modulated Positive mood, peaking at 14:15 hr (Sine component: p = .0012; Cosine component: p = .0001, Table 2) but not Negative mood (Sine component: p = .12; Cosine component: p = .13). Within-subject variability in light intensity did not significantly affect Positive mood (p = .11) or Negative mood (p = .80). Between- subject differences in average light exposure intensity did not relate to their average Positive or Negative mood (respectively p = .31; p = .52).

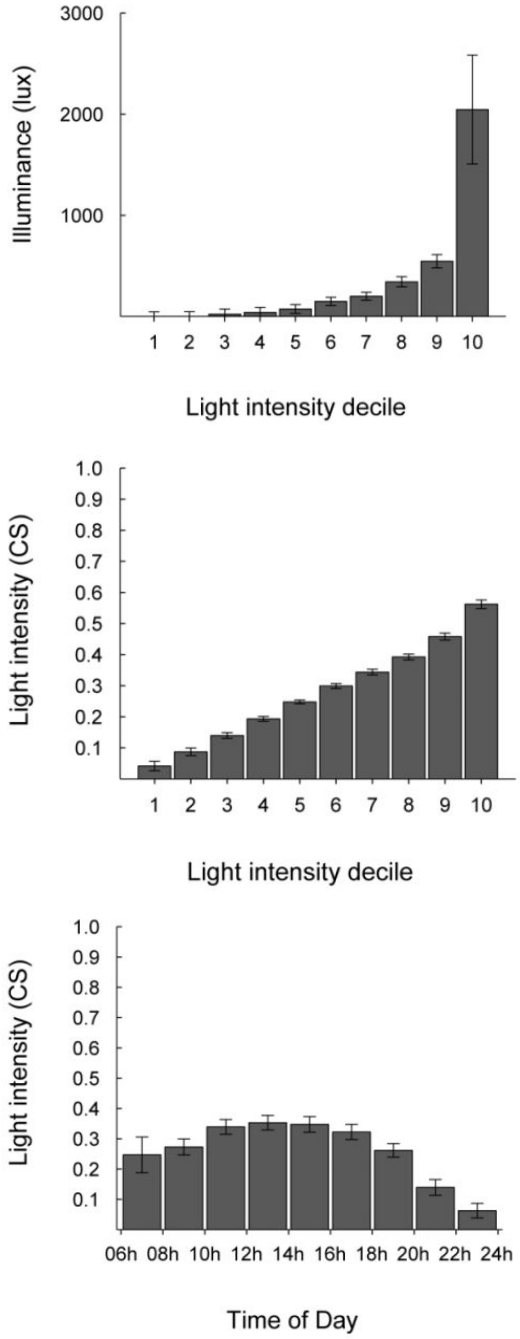

Figure 1. Range of recorded light level values. The upper and middle panels show illuminance distributions across ten deciles of the so-called circadian stimulus (CS) value of the illuminance, defined within each participant. The upper panel shows the nonlinear increase of illuminance values averaged in each decile. The middle panel shows how CS successfully linearizes the distribution across deciles of increasing light level. The lower panel shows the averages of the CS values, with the mid time of alarm-to-alarm intervals aggregated in two-hour time bins. Error bars indicate 95% confidence intervals. The number of observations in each interval is, respectively, 35, 151, 155, 135, 132, 142, 160, 134, and 60. Too few observations were available between 0:00 and 6:00 hr for useful visualization.

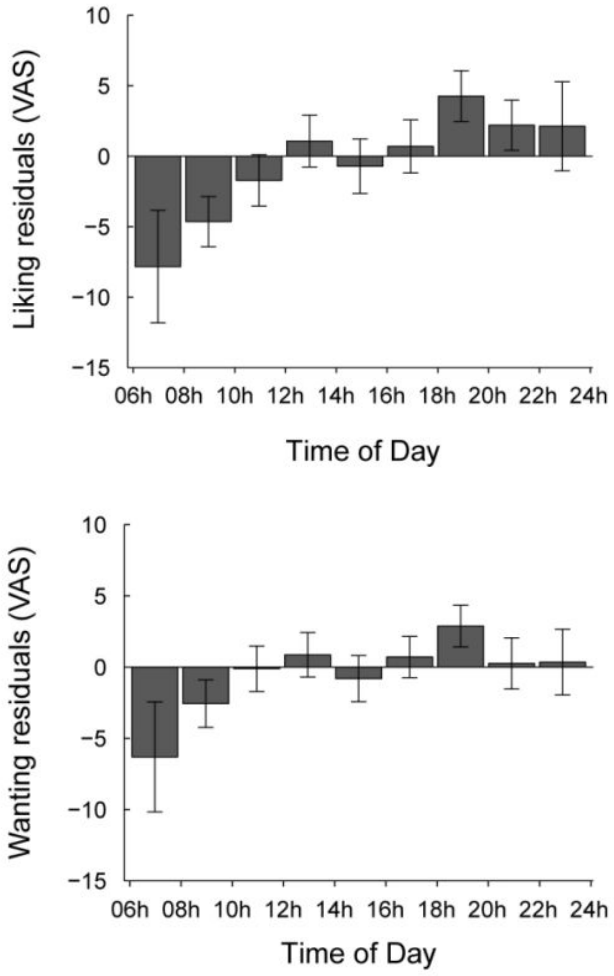

Figure 2. Subjective liking and wanting ratings peak around 18:00-19:00. Average subjectcentered ratings on Visual Analogue Scales with a total range of 100 for Liking (upper panel) and Wanting (lower panel) vary across time of day. Bars summarize the deviation from an individual's average rating (0 on the vertical axis), with the mid time of alarm-to-alarm intervals aggregated in two-hour time bins. Both plots show average residual ratings, after correcting for the effects of inter- and intra-individual differences in light exposure. Error bars indicate 95% confidence intervals. The number of observations in each interval is, respectively, 35, 151, 155, 135, 132, 142, 160, 134, and 60. Too few observations were available between 0:00 and 6:00 hr for useful visualization. Abbreviations: VAS = Visual Analogue Scale.

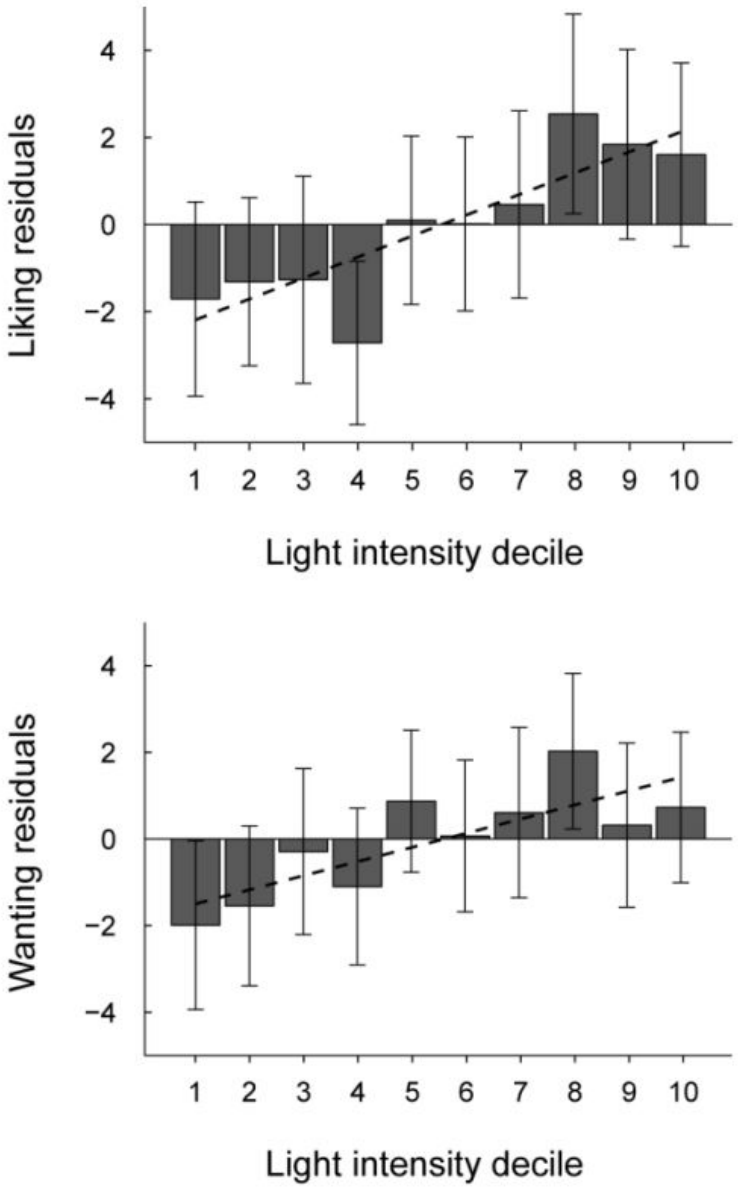

Figure 3. The intensity of environmental light significantly affects subjective liking and wanting ratings. Average subject-centered ratings on Visual Analogue Scales with a total range of 100 for Liking (upper panel) and Wanting (lower panel) increase with the level of light exposure. Bars summarize the deviation from individual's average rating (0 on the vertical axis), aggregated in ten deciles of increasing light level. Both plots show average residual ratings, after correcting for the effects of individual differences in light exposure and time of day. Error bars indicate 95% confidence intervals. Abbreviations: VAS = Visual Analogue Scale; CS = circadian stimulus.

Table 1. Fixed Effect Estimates of the Effects of Time of Day and Light Intensity on Subjective Wanting and Liking.

	Wanting			Liking		
	M	SE	95% CI	M	SE	95% CI
Intercept	39.3	3.1	[33.3, 45.5]***	35.9	2.6	[30.7, 41.1]***
Sin(TOD)	-2.7	0.5	[-3.8, -1.6]***	4.2	0.7	[-5.5, -2.9]***
Cos(TOD)	-0.1	0.6	[-1.3, 1.0]	0.9	0.7	[-0.5, 2.3]
$\text{LightIntensity}_{\text{subject-centered}}$	6.5	2.0	[2.7, 10.4]**	9.4	2.3	[4.8, 14.0]***

Note. Coefficient estimates of the optimal models are expressed as mean, standard error and 95% confidence intervals (CI). TOD = Time of day (rad). Time of day was converted to radians, where 24 hours equals 2π (0 and 2π represent midnight). Estimates were obtained from the distribution of 10,000 bootstrap replications. *p < .05, **p < .01, ***p < .001.

Table 2. Fixed Effect Estimates of the Effects of Time of Day on Positive and Negative Mood.

	Wanting			Liking		
	M	SE	95% CI	M	SE	95% CI
Intercept	56.1	2.2	[51.6, 60.6]***	22.1	2.4	[17.4, 26.9]***
Sin(TOD)	-1.7	0.5	[-2.7, -0.7]*			
Cos(TOD)	-2.7	0.5	[-3.6, 1.7]***			

Note. Coefficient estimates of the optimal models are expressed as mean, standard error and 95% confidence intervals (CI). TOD = Time of day (rad). Time of day was converted to radians, where 24 hours equals 2π (0 and 2π represent midnight). Estimates were obtained from the distribution of 10,000 bootstrap replications. *p < .05, **p < .01, ***p < .001.

Discussion

Based on the previous findings of direct and indirect projections of the retina of the eyes to reward-regulating brain structures, the present study aimed to evaluate immediate effects of light intensity on subjectively experienced liking and wanting, two major discriminable dimensions of the reward system. The Experience Sampling method was used to survey fluctuations in subjective liking and wanting across seven days and their relationship with fluctuating ambient light levels assessed using ambulatory monitoring. The results indicate that the subjective experience of both liking and wanting increases with increasing intensity of environmental light. Moreover, these experiences show a diurnal modulation, peaking in the late afternoon / early evening, and suggesting a possible circadian control.

To the best of our knowledge, this is the first study demonstrating acute effects of naturally occurring variation in light exposure on subjective liking and wanting. Importantly, the assessment of these basic properties of the reward system turned out to be more sensitive to light exposure than more traditional assessment of mood by rating adjectives which did not change significantly with varying ambient light levels. Interestingly, negative mood did not show a diurnal modulation.

Only few studies addressed acute effects of natural light exposure on mood outside of the laboratory environment. These studies used less dynamic sampling strategies (Espiritu et al., 1994; Jean-Louis et al., 2005), fixed time intervals (Einon, 1997) or events like social interactions (aan het Rot et al., 2008). The present study aimed to circumvent these limitations by using ES with quasi-random sampling while participants followed their normal routines, with no manipulations concerning their sleep-wake or leisure time.

A first limitation of the present study is that it addressed subjectively experienced liking and wanting only, which may or may not match implicit liking and wanting (Rømer Thomsen et al., 2015). Methods for momentary repeated assessment of implicit liking and wanting are however presently not available and would require extensive development and evaluation. A second limitation of the present study is that it did not assess individual differences in functionality of the neurobiological substrates that mediate the effect of light on the reward system, to evaluate their possible involvement in individual differences in the effect of light and time of day on liking and wanting. Indirect indicator variables are available to evaluate the functionality of ipRGCs (e.g. Wisse P. van der Meijden et al., 2015; W. P. van der Meijden et al., 2016) and the SCN (e.g. Harper et al., 2008; Kun Hu et al., 2016; K. Hu, Van Someren, Shea, & Scheer, 2009; E. J. W. Van Someren & Nagtegaal, 2007). A third and related limitation of the present study is that it assessed healthy young adults only. Future studies may evaluate how time of day and light levels modulate subjective liking and wanting in the aged population, where both retinal and circadian clock functioning become increasingly compromised (Swaab, Van Someren, Zhou, & Hofman, 1996; Turner, Van Someren, & Mainster, 2010).

The diurnal peak for subjective liking and wanting occurred in the early evening, whereas the diurnal peak intensity of environmental light exposure occurred in the early afternoon. These findings indicate additive effects of light intensity and time of day on subjective liking and wanting. It remains to be evaluated whether the effect of time of day is directly regulated by projections from the SCN to reward-related brain circuits, or secondary to e.g. diurnal changes in locomotor activity or body temperature that may affect these circuits as well (Dunn et al., 2010; Rolls, 2015). As visualized in Figures 2 and 3, and represented in the respective regression coefficients, the effect of naturally

occurring variation in environmental light intensity on liking and wanting is larger than the magnitude as the modulation of liking and wanting by time of day.

To the best of our knowledge, this is the first study to combine ambulatory monitoring of environmental light exposure with experience sampling of subjective liking and wanting. The method proved feasible and sensitive, and may provide a useful new tool to evaluate abnormalities in diurnal patterns and light sensitivity of subjective liking and wanting in disorders in which the systems regulating reward, emotion and stress are highly relevant, like addiction, depression and insomnia (e.g. Kent C. Berridge, Robinson, & Aldridge, 2009; DerAvakian & Markou, 2012; Koob & Volkow, 2010; Obayashi, Saeki, & Kurumatani, 2016; Parekh & McClung, 2016; Sousa, 2016; D. Stoffers et al., 2014; Diederick Stoffers et al., 2012; E. J. Van Someren et al., 2015; Wassing et al., 2016). An exciting possibility to address in future studies may subsequently be to evaluate the effect of timed manipulation of light exposure on such abnormalities.

Disclosure Statement

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Chapter 4: Bright environmental light ameliorates deficient subjective liking in insomnia: an experience sampling study

Bright environmental light ameliorates deficient subjective liking in insomnia: an experience sampling study.

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Keywords: Insomnia, reward, hedonia, mood, experience sampling, bright light, circadian rhythm

Abstract

Study Objectives: Altered comfort sensing and reduced gray matter volume in the orbitofrontal cortex of the brain in people suffering from Insomnia Disorder (ID) suggest compromised processes of motivation and hedonia. The Experience Sampling (ES) method was used to evaluate whether, in naturalistic conditions, people with ID differ from those without sleep complaints with respect to subjective wanting and liking, two major dimensions of the reward system. Since light affects brain circuits involved in affect and reward, ES was combined with ambulatory monitoring of light intensity fluctuations to evaluate their effect on subjective wanting and liking.

Methods: Participants with ID (n=17, 12 females, 56.8 ± 6.5 mean ± standard deviation years of age) and matched controls without sleep complaints (n=18, 12 females, 57.0 ± 8.6 years of age) were probed by a smartphone alarm to log their subjective wanting, liking and mood ten times a day for seven days. Using an ambulatory light recorder, light intensity exposure was sampled simultaneously and averaged over the intervals between subsequent ES alarms. Mixed effect models were used to evaluate how ID and varying light intensity affected subjective assessments.

Results: The results indicated significantly lower subjective Liking and Wanting in people suffering from ID, particularly at low environmental light intensity.

Conclusions: Wanting and liking, rather than more commonly used mood adjectives, showed an increased sensitivity to detect deficient hedonic and reward processing in insomnia during everyday life that may in part be rescued by exposure to bright environmental light.

Statement of Significance

A novel, more sensitive method of Experience Sampling revealed compromised hedonic and reward processes in insomnia during everyday life. Simultaneous ambulatory light monitoring showed that the deficiency was most marked at lower intensities of environmental light. Exposure to bright light may ameliorate a part of the daytime symptoms of insomnia.

Introduction

With prevalence estimates around 10%, insomnia is among the most frequent complaints in general practice. Insomnia Disorder (ID) is the second-most prevalent mental disorder[1], characterized by lasting problems falling asleep or waking up in the night or early morning, with subjective repercussions for daytime functioning. Over the past two decades, it has been recognized increasingly that symptoms of ID are not limited to sleep and involve a round-the-clock state of hyperarousal[2], both subjectively as indexed by e.g. tension, irritability, hypersensitivity and behavioral hyper-responsivity, as well as objectively as indexed by e.g. fast activity in the sleep and wake electroencephalogram (EEG), elevated cerebral glucose metabolism and enhanced cortical excitability[3-8].

Consensus assigns hyperarousal a key role in the pathophysiology of ID. Hyperarousal is a multidimensional construct, present around the clock in several behavioral, cognitive and electrophysiological assessments next to fragmented sleep.[9] Several studies have tried to find clues to the underlying mechanisms of hyperarousal.[3,4,10-12] The general tenet is that hyperarousal may result from chronic dysfunctional regulation of emotion, stress and reward. For a deeper understanding of the hyperarousal, it would therefore seem important to further our insight in the dysfunctional regulation of emotion, stress and reward in insomnia. This has for example been pursued using psychometric and physiological paradigms,[e.g. 10,13] and more recently with magnetic resonance imaging studies that linked hyperarousal to suboptimal functioning of a circuit involving the orbitofrontal cortex (OFC).[12] One of the better recognized OFC functions concerns the subjective experience of pleasantness, which has also been called 'hedonic evaluation' or Liking,[14,15] which in controlled lab studies seemed to be compromised in people suffering from insomnia.[16,17]

Liking is one of the two major discriminable dimensions of reward processing, next to another dimension that has been coined Wanting.[18,19] Whereas Liking refers to the pleasure dimension of a reward, Wanting represents the incentive motivation that promotes approach toward and consumption of rewarding stimuli. Although both have unconscious aspects as well, Liking can be subjectively experienced as feelings of pleasure or niceness, and Wanting as desires for incentives or declarative goals.[20] Wanting and Liking involve partially overlapping and partially discriminable brain circuits and may both contribute to anhedonia in psychiatric disorders.[20] Although Wanting and Liking may be processed in discriminable circuits of the brain, Baumeister[21] pointed out that the dimensions do not seem entirely orthogonal, i.e. they don't work independently (but see Kruglanski et al.[22] for a comment on their interrelatedness versus independence).

The first aim of the present study was to complement the relatively scarce functional observations of altered 'hedonic evaluation' or Liking in laboratory conditions in insomnia.[16,17] To do so we employed Experience Sampling (ES) study to evaluate whether people with ID experience less Liking, in everyday life, under naturalistic conditions. Since their relative contribution to anhedonia may differ across psychiatric disorders, we complemented the Experience Sampling survey on subjective liking by similar questions about subjective wanting. Compared to traditional retrospective self-reports Experience Sampling diminishes recall bias and selectivity by capturing current or recent behaviors. Furthermore, ecological validity is high compared to lab studies because subjective experiences can be described as they occur in the naturalistic environment.[23] Based on previous studies suggesting compromised OFC functioning in insomnia (see above and Discussion section), and given its involvement in Liking more than in Wanting,[14,15] we expected a particular deficiency in

Liking in everyday life in people suffering from ID: more so than in Wanting or in more traditional mood adjectives assessment.

A second aim of the present study was to evaluate how the naturalistically occurring variation in environmental light exposure affects subjective wanting and liking ratings in ID. Recent studies indicate that activation of the reward circuitry changes with light intensity,[24-26] which is likely to underlie the robust findings of favorable clinical effects of bright light on mood.[e.g. 27,28-31] Indeed, intrinsically photosensitive retinal ganglion cells (ipRGCs), that express the blue-light sensitive photopigment melanopsin and integrate information on environmental light intensity, have both direct and indirect projections to limbic areas involved in the regulation of mood and reward, including the lateral habenula, medial amygdala, and periaqueductal grey.[32-35] Whereas a handful of studies evaluated the effect of clinical application of bright light on sleep complaints in people suffering from ID,[36-40] studies on the immediate effect of dynamically changing light intensities on readouts of the reward system in ID are lacking. We therefore complemented the present ES study with wearable sensors for simultaneous ambulatory recording of naturalistic fluctuations in environmental light intensity, to assess how they affect subjective liking and wanting. Based on previous experimental work showing activation of the reward circuitry with bright light, we expected a positive association between naturally fluctuations in light intensity and subjective liking and wanting, both in cases and controls.

Methods

Participants

Participants were 17 people suffering from ID and 18 age- and sex-matched controls without sleep complaints (Table 1). Volunteers were recruited by advertisement, word of mouth and the Sleep Registry[41] and were screened using a dedicated online screening form followed by a telephone interview to verify their eligibility to participate in the study. All participants provided written informed consent. Initially, we searched for participants among people suffering from insomnia irrespective of their age. However, it turned out that very few of the responders were younger than 40 years of age. This is in accordance with the age-related increase in prevalence. Because we aimed for a relatively homogeneous sample with respect to age, we set inclusion criteria between 40 and 70 years of age and in addition self-acclaimed good health and working regular office hours. For the ID group self-reported sleep onset latency or wake after sleep onset greater than 30 min, and total sleep time less than 6.5 hours, for at least 6 months and for more than 3 nights per week at the time of intake. Exclusion criteria for all participants were diagnosed ocular pathology, drug abuse, excessive alcohol consumption (>10 glasses per week), crossing one or more time zones in the month prior to the study, current use of alertness-, sleep-, and thermoregulation-altering medication and any currently diagnosed sleep, neurological or psychiatric disorders other than ID according to the Sleep Registry implementation of the Duke Structured Interview for Diagnosing Sleep Disorders.[41,42] Prior to inclusion, volunteers were interviewed by telephone to verify the presence (in cases) or absence (in controls) of ID according to the third edition of the International Classification of Sleep Disorders.[43] All participants with ID reported suffering from complaints for more than 8 years. Group differences with respect to insomnia-related complaints were furthermore verified using the 7-item Insomnia Severity Index (ISI) questionnaire[44] and the Pittsburgh Sleep Quality Questionnaire (PSQI)[45] (Table 1). The Munich Chronotype Questionnaire (MCTQ)[46] was administered to evaluate group differences in midsleep on free days adjusted for average sleep need (MSF_{sc})[47] between ID and

controls. Participants received monetary compensation after study completion. The protocol was approved by the Ethics Committee of the VU University and Medical Center and performed in accordance with principles of the Helsinki Declaration.

Procedure

Volunteers participated in unconstrained ambulatory assessment in their natural environment for seven consecutive days. On the day prior to the start of the ambulatory assessment, subjects were introduced to the project, familiarized with the usage of a smartphone for Experience Sampling (ES) and attachment of the light sensors to their clothes.

Light Assessment

Participants received two dime-sized RGB multiband light sensors (Dimesimeter, also known as Daysimeter-D, Rensselaer Polytechnic Institute, Troy, NY, USA).[48,49] Photopic illuminance and the multiband light spectrum were sampled once every minute for seven consecutive days. Each sensor was integrated in a brooch. Subjects received two brooches. One of the brooches was pinned at chest level on the indoor clothing a participant chose to wear on each particular day from the moment they woke up until bedtime. The other brooch was pinned on the subject's outdoor jacket or coat at the same chest level and left there for all days this jacket or coat was used. The use of two brooches allows for continuous indoor and outdoor assessment: when the brooch on indoor clothing is covered by one's coat or jacket, the signal recorded from the brooch on the coat or jacket can be used to estimate environmental light exposure. Whether a coat was worn, could be assessed from the accelerometry signal integrated in each sensor.

Assessment of Liking and Wanting

Experience Sampling was used to repeatedly assess subjective liking and wanting. The method was implemented using MovisensXS software (Movisens GmbH, Karlsruhe, Germany) installed on a smartphone (Nexus 4, LG, Seoul, Korea). Participants were probed 8 times a day at quasi-random intervals timed between 8:00 and 22:00 hr, and were asked in addition to provide input after waking up and before bedtime. The interval between subsequent alarms ranged between 16 minutes and 3 hours. Preceding the first observation of each day, which was made immediately upon awakening, the subjects were asleep with eyes closed, usually in a dark bedroom. Hence the first observation of the day lacks variance in prior light exposure and was therefore not considered in the present study.

The assessment of explicit and implicit liking and wanting in humans is an area that is under development.[50-53] At the time of completing the design of the present study, we were not aware of previous work providing examples of their combined momentary assessment within the ES method. An interesting ES study on dieting and self-control of eating that was published later did however evaluate wanting ('desire') in great detail[54] and an even more recent study on Schizophrenia assessed appraisal of social interaction,[55] a specific example of liking that we included also in our approach. EVS and MK (as an expert on hedonia) discussed the domains to be included in a comprehensive assessment of liking, and developed questions for each domain phrased in such a way that it would fit the limited space on a smartphone screen and could as well be matched by a similarly phrased question about wanting in each domain. We surveyed both subjective liking and wanting at every prompt by six statements each, addressing the dimensions of "taste-smell", "bodily sensation", "watching/listening", "social interaction", "physical activity" and "receiving something".

Participants were asked to rate the extent to which each statement applied to them in the period between the current and previous alarm, using visual analogue scales with end points “not” and “very much” scaled to 0 and 100 respectively. The statements are shown below: liking (in Dutch: “genoot ik van…”) was queried first and immediately followed by questions on wanting (in Dutch: “had ik zin in…”).

Since the previous alarm, I enjoyed...

	not	very much
... a taste or smell	|----------	----------|
... a bodily sensation	|----------	----------|
... watching or listening	|----------	----------|
... interactions with other	|----------	----------|
... physical activity, being busy	|----------	----------|
... receiving something	|----------	----------|

Since the previous alarm, I wanted...

	not	very much
... a taste or smell	|----------	----------|
... a bodily sensation	|----------	----------|
... to watch or listen	|----------	----------|
... to interact with others	|----------	----------|
... physical activity, to be busy	|----------	----------|
... to receive something	|----------	----------|

Complementary assessment of more traditional mood adjectives

Whereas ES of liking and wanting has not previously been reported, several ES studies made use of positive and negative mood adjectives. It would be interesting to evaluate whether direct questions on wanting and liking are as sensitive to detect group differences and effects of light intensity as previously used positive and negative mood adjectives. We therefore queried at each alarm, and prior to the Wanting and Liking questions, positive and negative mood adjectives with relevance to insomnia as described in the Daytime Insomnia Symptom Scale (DISS).[56] The DISS consists of 19 visual analog scales, which load onto four factors labeled Alert Cognition, Sleepiness/Fatigue, Negative Mood and Positive Mood. The latter two factors were evaluated here.

Preprocessing

Light

Dimesimeter measurements were preprocessed with MATLAB 2014a (MathWorks Inc., Natick, Massachusetts, USA). The photopic illuminance and accelerometry signals of the sensors on the indoor and outdoor clothing were used to assess the validity of each light sample. Visual inspection indicated baseline noise in the absence of movements in the accelerometry signals. Values below the baseline noise floor were set to zero. Windows of at least 15-minutes without activity were marked as periods that the sensor was not worn[57] and excluded from analyses. Excluded were moreover all epochs without any light, indicating that the sensor was most likely covered. The remaining one-minute epochs were considered valid measurements. The time series of the two devices were

synchronized by means of the recorded timestamps. Sample-by-sample selection of light values of either indoor or outdoor clothing devices was accomplished as follows:

1) If only one of the sensors had a valid measurement, the sensor with the valid measurement was selected.

2) If the sensors on the indoor and outdoor clothing each simultaneously showed valid measurements, the sensor with the maximal photopic illuminance measurement was selected. This accounts for example for the situation in which an open jacket folds back to cover the outdoor clothing sensor, exposing the indoor sensor, while still selecting the outdoor sensor if a closed jacket covers the indoor sensor.

3) All other one-minute epochs were discarded.

The photopic illuminance and accelerometry was used only to assess the validity of the measurement and to choose which signal to use, but the co-recorded multiband spectrum was used for further analysis. The co-recorded multiband spectrum value of each valid photopic illuminance sample was nonlinearly transformed into a value between zero and one that represents the estimated downstream effect of the light intensity on the circadian system, as derived from its effectiveness to suppress melatonin (circadian stimulus, CS[58]), hereinafter referred to as 'light intensity'. Valid transformed light intensity values were averaged within each time interval between subsequent alarms. Intervals exceeding three hours were discarded and represented the intervals without valid data (e.g. the long interval prior to the first self-initiated ES assessment immediately upon waking). The resulting set of valid CS-transformed light intensity values averaged over the time interval between subsequent alarms was used for mixed effect regression analyses.

The CS transformation on light samples effectively linearized the otherwise nonlinearly distributed wide range of light illuminance values. For data description and visualization purposes only, the range of interval CS-transformed light intensity averages within each participant were assigned to ten deciles, and averaged across participants within each decile. The upper panel of Figure 1 shows the highly nonlinear decile distribution of untransformed interval illuminance averages, whereas the middle panel shows the linearized decile distribution of CS-transformed interval light intensity averages.

Liking, Wanting and complementary more traditional Positive and Negative mood adjectives

For each interval, a Liking and Wanting score was calculated by averaging the six visual analogue ratings in each of the domains assessed by experience sampling at the end of the interval. Likewise, for each interval, a DISS Positive Mood score was calculated by averaging the ratings on the five items 'Relaxed', 'Energetic', 'Calm', 'Happy' and 'Efficient', as well as a DISS Negative Mood score from the items 'Anxious', 'Stressed', 'Tense', 'Sad', and 'Irritable'. Intervals with incomplete or ignored experience sampling assessments were discarded.

Statistical analysis

In order to verify that people suffering from ID and controls did not differ systematically with respect to the time of year of assessment, possible group differences in circular means and standard deviations was evaluated using a Mardia-Watson-Wheeler test.[59]

Mixed-effect regression models were used to estimate how subjective Liking, Wanting, Positive mood and Negative mood changed with time of day and were affected by light intensity during the queried interval. The mixed-effect models accounted for the 3-level hierarchical structure of the data with a variable number of intervals (*i*) nested within a variable number of days (*j*), nested within subjects (*k*). Subject and days nested within subjects were specified as random factors to control for their associated intraclass correlation (ICC; i.e. random intercept).

Time of day, light intensity, ID, and the interaction effect of ID with light intensity and with time of day were included as regressors. Light intensity was added as a random effect to account for individual differences in the response to light intensity. The diagnosis of ID was included as a dichotomous variable with ID coded as 1 and control coded as 0.

Time of day was included in the models because diurnal rhythms have been demonstrated in reward behavior and neurophysiology[60] and subjective hedonic tone.[61] Time of day effects were estimated using the equivalent linear form of a 24-hour cosine curve[62] that combined the sine and the cosine of the midtime of each interval, expressed in radians where 24 hour equals 2π and 0 and 2π indicate midnight.

An additional separate model evaluated the modulation of light intensity by time of day and ID.

Intraclass correlation coefficients (ICC) were calculated for each model to understand how much of the variation in the dependent variable could be explained by the 3-level hierarchy of the data. Multilevel reliability coefficients were calculated to estimate the reliability of between-person differences and the reliability of within-person time variation of the items of the Positive and Negative mood scales of the DISS.[63]

Circular statistics were estimated using the "circular" package[64] and mixed-effects models were estimated using the "lme4" package[65] for R version 3.2.4.[66] The multilevel reliability coefficients and the ICCs were estimated using the "psych" package.[67] Summary statistics and 95% confidence intervals (CI) were calculated using a bootstrap procedure of 10,000 replications[68] using the "boot" package.[69] Significance of the effects of the independent variable on the dependent variable was obtained by calculating the fraction of 10,000 bootstrapped log-likelihood ratio (LRT) values that are larger or equal to the observed LRT value obtained from comparing the model with and without the independent variable.

The initially fitted models for the effect of time of day, light intensity, ID, and the interaction effects between ID and light intensity and between ID and time of day on subjective Liking, Wanting, Positive mood and Negative mood were as follows. Note that the last two non-significant interaction terms were omitted from the final model for Wanting and Liking:

$$Y_{ijk} = ß_{0ijk} + ß_1 * SineTimeOfDay_{ijk} + ß_2 * CosineTimeOfDay_{ijk} + ß_3 * LightIntensity_{ijk} + ß_4 * ID_k + ß_5 * ID_k * LightIntensity_{ijk} + ß_6 * ID_k * SineTimeOfDay_{ijk} + ß_7 * ID_k * CosineTimeOfDay_{ijk}$$

Where:

Y	is the dependent variable, either Liking, Wanting, Positive mood or Negative mood,
$_{i,j,k}$	subscripts indicate values measured over interval *i* of day *j* of participant *k*;
$ß_0$	is the intercept allowing for random variation over intervals *i*, days *j* and participants *k*;
$ß_1 – ß_2$	are the sine and cosine components of the linear form of a 24-hour cosine curve to capture diurnal variation;
$ß_3$	is the effect of light exposure;
$ß_4$	is the effect of a diagnosis of Insomnia Disorder (ID);
$ß_5$	is the interaction effect describing to what extent ID alters the effects of the within-subject-centered fluctuations in light exposure on the dependent variable;
$ß_6 – ß_7$	capture the interaction effect describing to what extent ID alters the sine and cosine components that model the diurnal variation

The fitted model for the modulation of light intensity by time of day and ID was as follows:

$$LightIntensity_{ijk} = ß_{0ijk} + ß_1 * SineTimeOfDay_{ijk} + ß_2 * CosineTimeOfDay_{ijk} + ß_3 * ID_k + ß_4 * ID_k * SineTimeOfDay_{ijk} + ß_5 * ID_k * CosineTimeOfDay_{ijk}$$

Where:

$LightIntensity_{ijk}$	is the dependent variable,
$_{i,j,k}$	subscripts indicate values measured over interval *i* of day *j* of participant *k*;
$ß_0$	is the intercept allowing for random variation over intervals *i*, days *j* and participants *k*;
$ß_1 – ß_2$	are the sine and cosine components of the linear form of a 24-hour cosine curve to capture diurnal variation;
$ß_3$	is the effect of a diagnosis of Insomnia Disorder (ID);
$ß_4 – ß_5$	capture the interaction effect describing to what extent ID alters the sine and cosine components that model the diurnal variation

Results

We collected a total of 2205 alarms. We discarded any incomplete surveys (dismissed or ignored by the participant; 4.4%), those with an excessively long prior time interval since the last alarm (>3 hrs, the maximal time between random intervals; 8.3%) and those with evidence of the light sensor not being worn (7.3%). The remaining 1764 alarms were included in the analysis, indicating that on average 80% of the alarms contained valid data.

Assessments were performed across the year and covered all months except for January, September and December. The group circular means and standard deviations were 11 June ± 69 days in people suffering from ID and 3 June ± 78 days in controls and did not differ significantly (Mardia-Watson-Wheeler W = 0.04, P = 0.98).[59]

Light exposure

There was no group difference in overall light exposure between ID and controls (P = 0.57; Figure 1). Light intensity was on average 0.31 ± 0.01 [0.29 0.34] for ID and 0.29 ± 0.02 [0.25 0.32] for controls. Diagnosis by Time of Day interaction terms indicated that people with ID differed slightly from controls with respect to the timing of their diurnal light exposure profile (ID interaction with the Sine component: -0.03 ± 0.01 [-0.05 -0.01] (effect estimate ± standard error of the estimate [95% confidence interval), P = 0.012; ID interaction with the Cosine component: -0.04 ± 0.01 [-0.06 -0.02], P = 0.001). Light intensity peaked at 13:26 hour in ID and slightly earlier, at 13:14 hour, in controls.

Wanting and liking

There were highly significant group differences in overall subjective Liking and Wanting between ID and controls. People with ID rated significantly lower both on subjective Liking (P = 0.001) and on subjective Wanting (P = 0.0004, Table 2). Average Liking was 34.9 ± 2.3 [30.4 39.4] for ID and 44.6 ± 2.8 [39.0 50.1] for controls. Average Wanting was 34.1 ± 2.2 [29.8 38.5] for ID and 45.1 ± 2.9 [39.2 50.8] for controls. Diagnosis by Time of Day interaction terms indicated that people with ID did not differ from controls with respect to the amplitude or phase of the diurnal 24-hour profiles in Liking or Wanting (all ID·Sine and ID·Cosine component terms were $0.26 < P < 0.90$). Therefore, these terms were excluded from the final mixed effect regression models. Thus, consistent across all participants, time of day significantly modulated Liking, peaking at 16:05 hour (Sine component: $P < 0.0001$; Cosine component: P = 0.0003, see Figure 2). Likewise, time of day modulated Wanting resulting in a peak at 15:40 hour (Sine component: $P < 0.0001$; Cosine component: $P < 0.0001$).

A significant ID by light intensity interaction effect (P = 0.04) indicated that variability in light exposure significantly affected the experience of Liking only in ID. A similar interaction effect could not be found for Wanting (P = 0.09). As visualized in Figure 3, controls without sleep complaints remained at average levels of subjective Wanting and Liking irrespective of light intensity, whereas higher light intensities partly ameliorated the overall lower subjective Liking but not Wanting in participants suffering from insomnia. We moreover evaluated effects of the severity (ISI) and duration (DSISD) of insomnia among participants diagnosed with ID. Whereas both Wanting (P = 0.03) and Liking (P = 0.02) increased significantly with light, the effect of light on Wanting (P = 0.19) nor Liking (P = 0.20) was not moderated by severity (ISI*CS interaction). Wanting and Liking were not significantly associated with the duration of insomnia, nor was the effect of severity on Wanting and Liking (P = 0.10, P = 0.07, P = 0.17 and P = 0.24, respectively).

Wanting and Liking yielded ICCs of 0.54 ± 0.05 [0.45 0.63] and 0.49 ± 0.05 [0.40 0.58], respectively, indicating about equal within-subject and between-subject contributions to the variance in Wanting and Liking.

Positive and Negative Mood

There were no differences in overall Positive or Negative mood between ID and controls (respectively P = 0.81; P = 0.46).

Diagnosis by Time of Day interaction terms indicated that people with ID differed from controls with respect to the diurnal profile of Positive mood and Negative mood (Table 3, Figure 4). Positive mood peaked at 15:14 hour for ID and 12:13 for controls (ID interaction with Sine component: P = 0.003; ID interaction with Cosine component: P = 0.37). Likewise, time of day modulated Negative mood resulting in a peak at 06:31 hour for ID and 15:33 for controls (ID interaction with Sine component: P = 0.0001; ID interaction with Cosine component: P = 0.97).

No ID by light intensity interaction effect was present for Positive mood and Negative mood (Figure 5, P = 0.14 and P = 0.45, respectively).

Positive mood and Negative mood yielded ICCs of 0.73 ± 0.04 [0.64 0.81] and 0.62 ± 0.04 [0.53 0.71], respectively, indicating a larger between-subject than within-subject contribution to the variance in Positive and Negative mood. The multilevel reliability coefficients for Positive mood and Negative mood are shown in Table 4. The between-person reliability is higher than the within-person reliability indicating that the scales are better at discriminating between-person differences than within-person differences.

Table 1 – Characteristics of participants

	Control (n = 18)	Insomnia Disorder (n = 17)	P
Age (yr)	57.0 ± 8.6	56.8 ± 6.5	0.83
Sex (Female/Male)	12/6	12/5	1
Body Mass Index (kg/m^2)	24.4 ± 4.0	24.6 ± 3.6	0.74
ISI	4.4 ± 3.4	17.0 ± 4.6	< 0.0001
DIS	0.5 ± 0.7	2.1 ± 1.5	< 0.0001
DMS	0.4 ± 1.0	3.2 ± 1.1	< 0.0001
EMA	0.4 ± 0.6	2.8 ± 1.1	< 0.0001
PSQI	3.9 ± 1.7	9.9 ± 3.2	< 0.0001
MCTQ (HH:MM)	04:09 ± 00:41	03:15 ± 00:57	0.003

Mean values ± SD (range) are shown. ISI, Insomnia Severity Index; DIS, Difficulty Initiating Sleep; DMS, Difficulty Maintaining Sleep; EMA, Early Morning Awakening; PSQI, Pittsburgh Sleep Quality Index; MCTQ, Munich Chronotype Questionnaire. DIS, DMS and EMA represent the frequency of the complaint experienced over the last 2 weeks as assessed by the ISI at recruitment.

Table 2. – Model estimates of the effects of time of day, light intensity and insomnia disorder on subjective wanting and liking.

	Wanting			Liking		
Fixed Effects	β	SE	CI	β	SE	CI
Intercept	41.6	2.6	[36.5 46.7]***	41.5	2.6	[36.3 46.7]***
sin(TOD)	-4.5	0.5	[-5.6 -3.5]***	-5.5	0.6	[-6.7 -4.4]***
cos(TOD)	-3.2	0.7	[-4.6 -1.8]***	-3.0	0.8	[-4.5 -1.5]***
CS	4.5	5.4	[-6.0 15.0]	2.1	5.1	[-7.9 12.1]
ID	-14.8	3.7	[-22.3 -7.5]***	-14.0	3.8	[-21.5 -6.6]**
ID · CS	12.4	7.2	[-1.5 26.5]	14.2	6.7	[1.1 27.3]*
Random Effects	σ	SE	CI	σ	SE	CI
$Intercept_{subject}$	10.1	1.5	[7.2 13.1]	10.1	1.5	[7.2 13.1]
$Intercept_{subject/day}$	6.9	0.5	[5.9 7.8]	6.4	0.5	[5.4 7.4]
$CS_{subject}$	18.6	3.0	[12.6 24.2]	16.3	2.9	[10.4 21.9]
Residual	11.8	0.2	[11.4 12.2]	12.9	0.2	[12.4 13.4]
ICC	0.55	0.05	[0.46 0.63]	0.49	0.05	[0.40 0.58]

Mean values ± SE [95% CI] are shown. CS, circadian stimulus; TOD, Time Of Day (rad); ID, Insomnia Disorder. *P < 0.05; **P < 0.01; ***P < 0.001. For subjective wanting and liking the optimal models are shown. TOD was converted to radians, where 24 hours equals 2π. Insomnia Disorder (ID) was included in the model as a dichotomous variable coded as 0 for controls and 1 for cases.

Table 3 – Model estimates of the effects of time of day, light intensity and insomnia disorder on positive and negative mood.

	Positive Mood			Negative Mood		
Fixed Effects	β	SE	CI	β	SE	CI
Intercept	57.7	3.1	[51.5 63.8]***	16.5	2.1	[12.3 20.6]***
sin(TOD)	-0.2	0.6	[-1.3 0.9]	-0.5	0.5	[-1.5 0.5]
cos(TOD)	-3.3	0.7	[-4.7 -1.8]***	-0.4	0.7	[-1.8 0.9]
CS	2.5	3.5	[-4.4 9.3]	-0.3	2.7	[-5.5 5.0]
ID	-0.5	4.5	[-9.2 8.4]	-1.1	3.0	[-7.1 5.0]
ID · CS	7.2	4.9	[-2.5 16.8]	-2.8	3.7	[-10.1 4.6]
ID · sin(TOD)	-2.5	0.8	[-4.0 -1.0]**	3.1	0.7	[1.8 4.5]***
ID · cos(TOD)	0.9	1.0	[-1.1 3.0]	0.05	1.0	[-1.8 2.0]
Random Effects	σ	SE	CI	σ	SE	CI
$Intercept_{subject}$	12.7	1.7	[9.5 16.1]	8.3	1.2	[6.2 10.7]
$Intercept_{subject/day}$	5.5	0.4	[4.8 6.3]	5.2	0.4	[4.5 5.9]
$CS_{subject}$	10.1	2.0	[6.1 13.8]	5.7	1.8	[1.4 8.9]
Residual	8.6	0.2	[8.2 8.9]	7.9	0.2	[7.6 8.2]

Mean values ± SE [95% CI] are shown. CS, circadian stimulus; TOD, Time Of Day (rad); ID, Insomnia Disorder. *P < 0.05; **P < 0.01; ***P < 0.001. Time of day (TOD) was converted to radians, where 24 hours equals 2π. Insomnia Disorder (ID) was included in the model as a dichotomous variable coded as 0 for controls and 1 for cases.

Table 4. – Variance decomposition and between- and within-person reliability estimates of positive and negative mood.

Variance component	Positive Mood	%	Negative Mood	%
σ^2_{PERSON}	169	38.1	77	29.7
$\sigma^2_{TIME(PERSON)}$	73	16.4	67	25.9
$\sigma^2_{RESIDUAL}$	202	45.5	116	44.8
Total	444	100	259	100
R_{KRN}	0.99		0.99	
R_{CN}	0.64		0.74	

Variance components are presented as absolute values and percentages. σ^2_{PERSON} represents the between-subject variance. $\sigma^2_{TIME(PERSON)}$ represents the within-subject variance. $\sigma^2_{RESIDUAL}$ represents the error variance. R_{KRN} represents the estimate of between-subject reliability, assuming that items are nested within times, which are nested within participants. R_{CN} represents the estimate of the nested within-subject reliability.

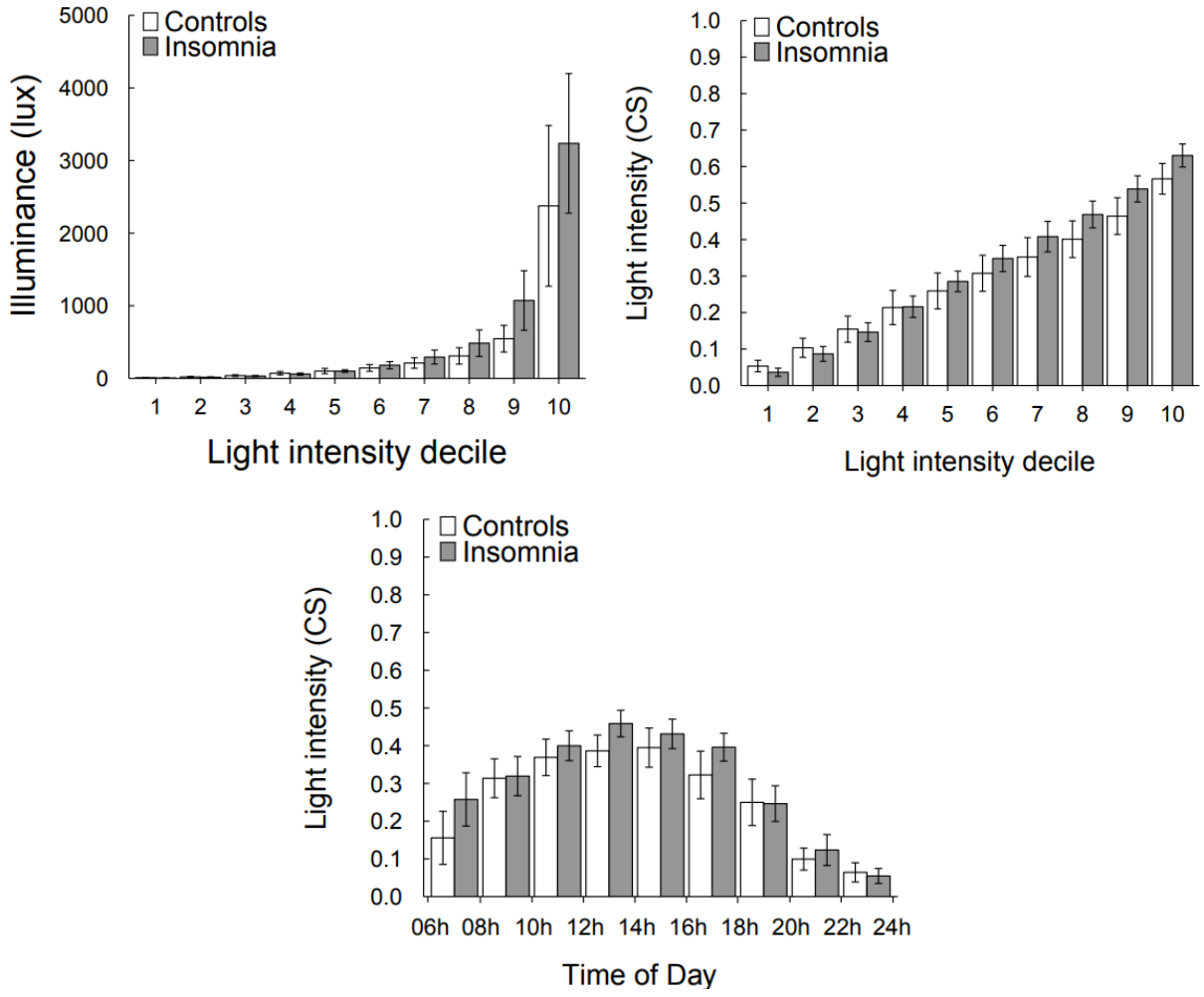

Figure 1. Range of recorded average light intensities in ID (gray bars) and controls (white bars). The upper and middle panels show distributions across ten deciles defined within each participant. The upper panel shows the nonlinear increase of photopic illuminance values averaged in each decile. The middle panel shows how the 'circadian stimulus (CS)'-transformation linearizes the distribution across deciles of increasing intensities. The lower panel shows the within-subject averages of CS-transformed light intensity values, with the mid time of alarm-to-alarm intervals aggregated in two-hour time bins. Error bars indicate 95% confidence intervals. The numbers of observations in each time interval were, respectively, 34, 162, 117, 105, 88, 105, 118, 98 and 31 for the control participants and 63, 141, 110, 109, 103, 99, 119, 115 and 36 for participants suffering from insomnia. Too few observations were available between 0:00 and 6:00 hour for useful visualization. There was no group difference in overall light exposure (P = 0.57).

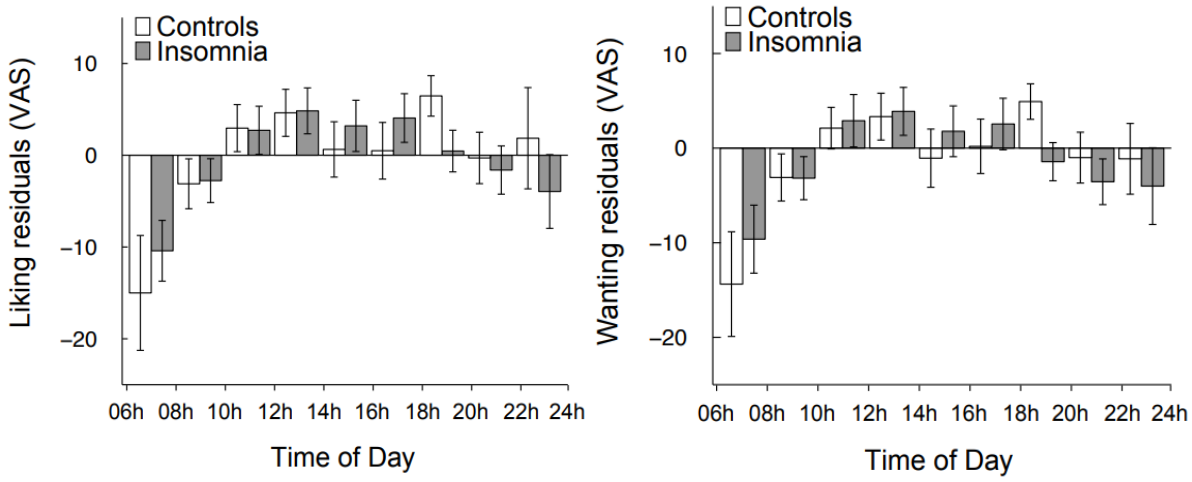

Figure 2. Subjective liking and wanting ratings across the day show a peak in the afternoon. Subjective ratings on Liking (upper panel) and Wanting (lower panel) vary across time of day in participants suffering from ID (gray bars) and controls (white bars). Data are aggregated in two-hour time bins according to the mid time of the intervals between subsequent alarms. In order to be able to visualize time of day effects only, both plots show residual ratings, after adjusting for the effects of intensity of circadian stimulus. Error bars indicate 95% confidence intervals. The numbers of observations in each time interval were, respectively, 34, 162, 117, 105, 88, 105, 118, 98 and 31 for the control participants and 63, 141, 110, 109, 103, 99, 119, 115 and 36 for participants suffering from insomnia. Too few observations were available between 0:00 and 6:00 hour for useful visualization. Mixed effect regression analysis fitting a linearized 24-hour cosine function indicated significant diurnal variation in both Liking and Wanting that did not differ between ID and controls, respectively peaking at 15:40 hour and 16:05 hour. Abbreviations: VAS = Visual Analogue Scale.

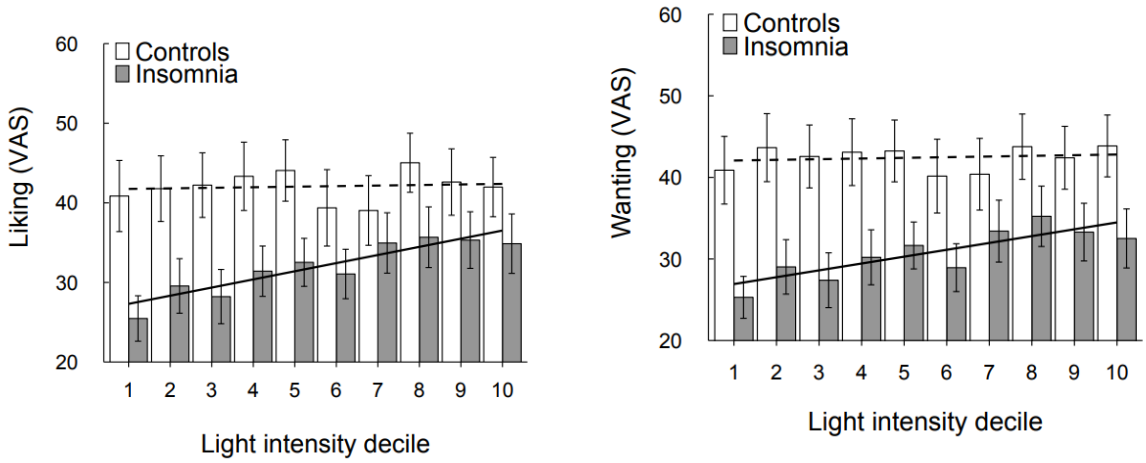

Figure 3. Higher environmental light intensities partly ameliorate low subjective liking but not wanting ratings in insomnia. Average subjective ratings on Liking (upper panel) increase with light intensity only in participants suffering from insomnia disorder (gray bars, solid line) but not in control subjects (white bars, dashed line). Wanting (lower panel) shows a similar but non-significant trend. Bars summarize average ratings, aggregated in ten deciles of increasing CS-transformed light intensity ranges defined within each participant. Error bars indicate 95% confidence intervals. Abbreviations: VAS = Visual Analogue Scale.

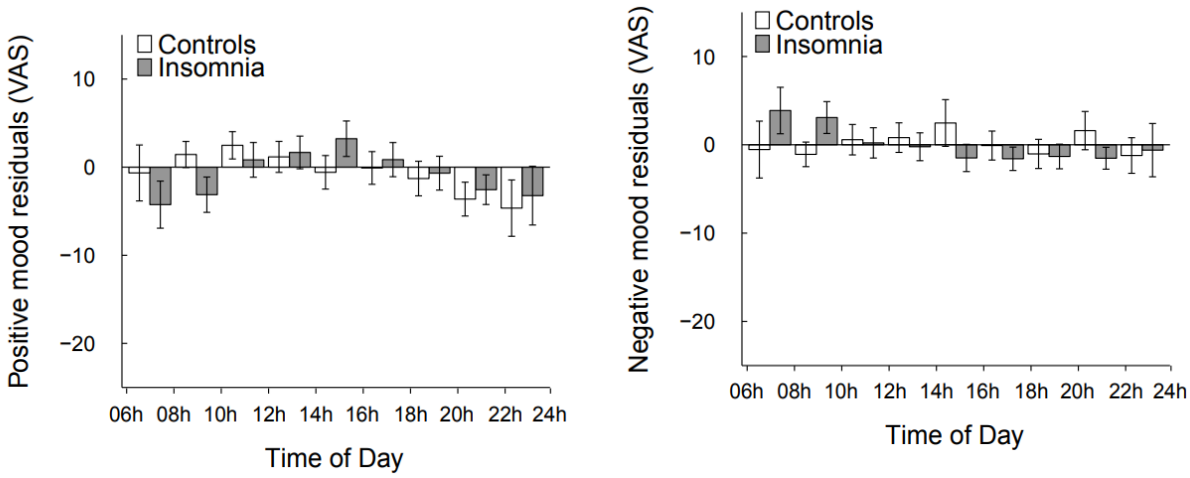

Figure 4. The diurnal peak in positive mood and negative mood ratings differ between controls and insomnia. Average subject-centered ratings on Positive mood (upper panel) and Negative mood (lower panel) vary across time of day in participants suffering from ID (gray bars) and controls (white bars). Data are aggregated in two-hour time bins according to the mid time of the intervals between subsequent alarms. In order to be able to visualize time of day effects only, both plots show residual ratings, after correcting for the effects of CS-transformed light intensity. Error bars indicate 95% confidence intervals. The numbers of observations in each time interval were, respectively, 34, 162, 117, 105, 88, 105, 118, 98 and 31 for the control participants and 63, 141, 110, 109, 103, 99, 119, 115 and 36 for participants suffering from insomnia. Too few observations were available between 0:00 and 6:00 hour for useful visualization. Mixed effect regression analysis fitting a linearized 24-hour cosine function indicated significant diurnal variation in both Positive mood and Negative mood that differed between ID and controls. Positive mood peaked at 15:14 hour in ID and 12:13 hour in controls. Negative mood peaked at 06:31 hour ID and 15:33 hour in controls. Abbreviations: VAS = Visual Analogue Scale.

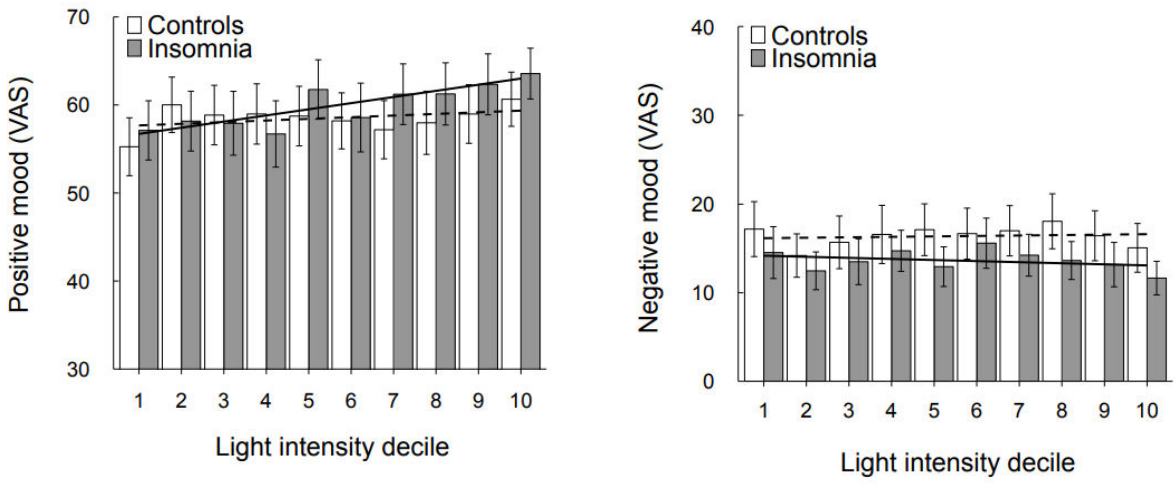

Figure 5. Positive and negative mood ratings of people suffering from insomnia and control subjects do not change with more intense environmental light. Average subjective ratings on Positive mood (upper panel) and Negative mood (lower panel) do not significantly change with light intensity in participants suffering from insomnia disorder (gray bars, solid line) or control subjects (white bars, dashed line). Bars summarize average ratings, aggregated in ten deciles of increasing CS-transformed light intensity ranges defined within each participant. Error bars indicate 95% confidence intervals. Abbreviations: VAS = Visual Analogue Scale.

Discussion

Previous findings suggested that people suffering from insomnia may have a compromised hedonic capacity that could involve structural deviations in the orbitofrontal cortex. Based on these findings, the present study aimed to evaluate whether, during everyday life, people suffering from insomnia differ from those without sleep complaints with respect to subjectively experienced liking and wanting, two major dimensions of the reward system. Moreover, based on the previous findings of direct and indirect projections of the retina of the eyes to reward-regulating brain structures, the second aim of the present study was to evaluate immediate effects of light intensity on subjectively experienced liking and wanting, and whether possible effects would differ between people suffering from insomnia and those without sleep complaints.

The Experience Sampling method was used to survey fluctuations in subjective liking, wanting and more commonly used positive and negative mood adjectives across seven days. The association of these fluctuations with changing ambient light intensities was assessed using ambulatory monitoring. The results indicated that people suffering from insomnia experience significantly less liking and wanting than those without sleep complaints. Interestingly, some recent brain imaging studies have also found deviations in the brain circuitry involved in liking and wanting, or more general, the regulation of emotion, stress and reward. Notably, insomnia severity was found to be associated with volume reduction in the orbitofrontal cortex (OFC),[70-72] a key structure in hedonic evaluation (liking). OFC volume was moreover found to be positively associated with the ability to maintain or resume sleep in the morning in people without sleep complaints[73,74] and with perceived sleep quality in veterans.[75] In elderly people, OFC volume was negatively associated with sleep fragmentation[76] which is a key characteristic of insomnia as well.[10,77,78] One study found that OFC volume correlated with the severity of insomnia but not with its duration.[13] It was therefore suggested that a low volume could indicate suboptimal functioning that could contribute to insomnia and hyperarousal.[12] Given the role of the orbitofrontal cortex in Liking, reduced gray matter volume may be involved in the deficient sensing of comfort and other pleasant experiences that has been reported before in insomnia in a controlled laboratory study[17] as well as during a eyes-closed resting state recorded at home.[16]

In turn, insufficient sensing, integration, and updating of hedonic signals by the orbitofrontal cortex can result in an insufficient excitatory output to, and activation of, its major projection area, the caudate nucleus, which has an important role in dampening cortical arousal.[12] Using functional MRI, deficient activation of this 'brake' on cortical excitability has been demonstrated in insomnia, especially in those with a more pronounced OFC volume reduction, and proposed to thus contribute to hyperarousal.[12]

The deficient wanting and liking in people suffering from insomnia could not be attributed to a lower overall average exposure to ambient light intensities, which did not differ between cases and controls. Importantly, whereas fluctuations in ambient light intensity do not affect the subjective experience of liking and wanting in those without sleep complaints, high intensities of ambient light ameliorated the compromised experience of liking of people suffering from insomnia. A third finding of the present study is that the subjective experience of liking and wanting changes in the course of the day and peaks in the late afternoon. This suggests the presence of a diurnal rhythm of liking and wanting. A recent laboratory study with a more limited number of time points (10:00, 14:00 and 19:00 hours) in healthy young males supports the afternoon peak for wanting but may have been too sparsely

sampled to detect a diurnal rhythm was observed for liking.[79] Whether the diurnal rhythm of liking and wanting is endogenously driven cannot be determined from the present observational field study and remains to be determined in well-controlled laboratory studies. A fourth observation of the present study is that Experience Sampling of fluctuations in subjective liking and wanting seems more sensitive to reveal group differences and effects of light intensity than more commonly used positive and negative mood adjectives.

To the best of our knowledge, this is the first study aiming to measure the acute effects of natural light exposure on subjective liking and wanting. Only few studies addressed acute effects of natural light exposure on mood outside of the laboratory environment. These studies used less dynamic sampling strategies,[80,81] fixed time intervals[82] or were limited to specific events like social interactions.[83] The present study aimed to circumvent these limitations by using quasi-randomly timed Experience Sampling of liking and wanting. No manipulations concerning sleep-wake or leisure time schedules were undertaken and participants followed their normal routines.

A first limitation of the present study is that it addressed subjectively experienced liking and wanting only, which may or may not match *implicit* liking and wanting.[20] Methods for brief repeated ambulatory assessment of implicit liking and wanting are however presently not available. A recent lab study however found converging support for an afternoon peak in implicit wanting.[79] A second limitation of the present study is that it did not assess individual differences in functionality of the neurobiological substrates that mediate the effect of light on the reward system and may be compromised with advancing age,[84,85] to evaluate their possible involvement in individual differences in the effect of light and time of day on liking and wanting. Indirect indicators are available to evaluate the functionality of ipRGCs[e.g. 86,87,88] and the SCN.[e.g. 89,90-92] A third limitation may be that the age-range of our sample, which is based on the biased entry of people suffering from insomnia with a somewhat advanced age, because of the naturally occurring increased prevalence with aging. In order to attain a homogeneous sample, we restricted the age range to 40-70 years, and targeted matched controls in the same age range. We thus did not specifically target a study on aging, rather a case-control study on insomnia.

The diurnal peak for subjective liking and wanting occurred in the middle of the afternoon, somewhat later than the early afternoon peak for environmental light exposure. These findings suggest that the effect of light intensity on subjective liking and wanting in people suffering from insomnia is additive to the effect of time of day.[79,93] Although the diurnal peak occurs in the middle of the afternoon, Figure 2 reveals that the actual rating are lower around this time, suggesting a post-lunch decrement in wanting and liking which is more pronounced in controls than in ID. As visualized in Figure 3, even under the highest naturally occurring light intensities, the subjective liking and wanting of people suffering from insomnia does not match the subjective liking and wanting of those without sleep complaints.

Whereas we have interpreted the findings as supporting a causal contribution of light to wanting, liking and mood, a reverse explanation could be considered as well. Possibly, if people experience stronger wanting, liking or positive mood, they might be more likely to subsequently experience bright light, e.g. by going outdoors. We therefore evaluated post-hoc whether this possibility would fit the data better than the model we fitted to the data to evaluate the contribution of light to subsequent wanting, liking and mood. However, in the models evaluating whether wanting, liking or mood have predictive value for subsequent light exposure in addition to the predictive value of light exposure

itself for subsequent light exposure, only the interaction effects of ID by positive mood ($P = 0.05$) and ID by Liking ($P = 0.06$) were borderline significant, but none of the other main or interaction effects ($0.30 < P < 0.98$). The finding suggests that people with insomnia are also somewhat more likely to expose themselves to bright light after they experience a more positive mood.

Still, the findings provide further support the importance of naturalistic exposure to bright light especially in people with vulnerable sleep. The findings moreover suggest that the therapeutic use of bright light on the functionality of the reward system does not have to be limited to the treatment of depression. It is well known that the complaints of people with insomnia are not limited to their sleep, and the present study provides further support for suboptimal functioning of reward processing.

Some studies in the general population pointed out the importance of naturalistic light exposure for those with vulnerable sleep. In a large observational study on workers of a transportation company, one third of the 13,000 participants experienced no light exposure during working hours and experienced more insomnia than their colleagues who were exposed to natural light.[94] A similar smaller observational study found similar differences with respect to sleep quality but, interestingly, also significantly higher self-reported vitality and a trend toward higher daytime activity in those with better light exposure.[95] The latter findings are compatible with that of an activating effect of light to motivational systems. Studies in healthy elderly people[96] and elderly insomniacs[97] support favorable effects of bright light interventions on well-being and daytime functioning also at advanced age.

Although not considered in the present study, the timing of light exposure may be particularly important. A recent study found an association between both higher intensities of nighttime light exposure and lower intensities of morning light exposure and weight gain.[98] These effects were independent of sleep-wake parameters. Combined with a recent finding that hedonic evaluation is an important factor in over-eating, those with poor sleep and suboptimal functioning of reward processing may be at an increased risk of obesity,[99] that might in part be mitigated by bright light exposure.

In conclusion, by using novel and more sensitive assessment tools, the present study indicates relevance during everyday life of previous suggestions of suboptimal reward processing in people suffering from insomnia,[12,16,17] as well as of previous suggestions that light affects the reward circuitry[24-26] that could be mediated by projections from photosensitive retinal ganglion cells in the eye to limbic areas including the lateral habenula, medial amygdala, and periaqueductal grey.[32-35] Our findings provide further support for considering the addition of bright light to a multi-component treatment of insomnia.[7]

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Chapter 5: Summary, General Discussion and Perspectives

Light exposure leads to changes in mood via two hypothesized pathways. An indirect pathway is mediated by changes in sleep and circadian rhythms (e.g., effects relayed by the master clock in the suprachiasmatic nucleus [SCN]). The direct pathway entails light altering mood through ipRGC projections to brain structures that regulate reward and motivation. Three experimental chapters were designed to study a broad range of contexts in which light modulates mood-related behavior. Two of these contexts were pathological scenarios, namely behavioral and biochemical alterations secondary to photoperiodic changes in an animal model and primary insomnia in a human population. The deviation of behaviors in disease is helpful in elucidating the normal functioning of these behaviors. Given that mood (as well as the intimately linked concepts of reward and affect) is a subjective as well as an objective phenomenon, a combination of animal and human models circumvents limitations of each model working alone. Animal models allow for ethical invasive exploration of brain substrates of these behavioral processes aiming at objectivity. Human models allow for the exploration of the subjectivity of affect, here examined in dynamic real-time conditions.

The interactions of these modalities and pathways are discussed below. As well, any intricacies which were not addressed in the individual chapters are also mentioned, such as the neuroanatomical background upon which these pathways are built on. First, a summary is given of the data presented in the previous chapters. In the subsequent sections we will then focus on the different issues, conclusions and new questions raised by our results in the context of other studies. We will wrap up with the introduction of an overarching framework which might count the reward effects of light as part of homeostasis. Future directions will be discussed in the last sections.

Summary

Chapter 2 showed behavior and brain physiology alterations in *Arvicanthis ansorgei* (a diurnal rodent) secondary to exposure to winter-like photoperiodic conditions and after light exposure early in the day or late in the day. After 6 weeks of exposure to shortened days with diminished light intensity (winter-like photoperiod, LD8:16h), subjects expressed (1) alterations in the synchronization of locomotor activity rhythms to the light–dark cycle, (2) alterations in day–night activity of dopaminergic neurotransmission in the nucleus accumbens and the dorsal striatum and (3) day-night alterations in clock gene expression in the suprachiasmatic nucleus. Dopamine disturbances were reversed in animals exposed to daily light at early or late day. Moreover, *Per2* gene expression in the SCN was also affected by light exposure at late day in winter-like exposed animals. However, the pulses given late in the day resulted in correction of the phase advancement whereas those given early in the day did not.

The study in **chapter 3** elucidated the direct effects of light on mood in natural environments, in healthy young participants. A study modality known as experience sampling (aan het Rot et al., 2008) was implemented to repeatedly assess subjective affect using two outputs of the reward system: wanting and liking. Experience sampling was complemented by simultaneous ambulatory recording of natural fluctuations in ambient light in order to correlate them with the aforementioned mood ratings. Mixed effect models revealed that higher liking and wanting scores were found after exposure to more intense light within the interval prior to the assessment, even when accounting for circadianity in the mood ratings. Diurnal peaks for subjective liking and environmental light exposure occurred in different timings, indicating that light and circadianity are independent factors when determining

affect. Therefore, independent pathways are suggested to exist for determining direct effects of light on mood and indirect effects as mediated by circadian rhythms.

In **chapter 4**, experience sampling was used once again to study the effects of light on mood ratings in elderly populations with and without insomnia. The results indicated that people suffering from insomnia experience significantly less liking and wanting than those without sleep complaints. Whereas fluctuations in ambient light intensity did not affect the subjective experience of liking and wanting in those without sleep complaints, high intensities of ambient light ameliorated a compromised experience of liking and wanting of people suffering from insomnia. Average ambient light intensities did not differ between cases and controls. The results suggest that insomniacs have a deficit in feeling, recognizing or reporting subjective affect, which is partly restored by bright environmental light.

I. Study of the indirect pathway of the reward effects of light

a. Behavioral changes secondary to exposure to a winter-like photoperiod

In order to study the biochemical substrates of light-induced changes on the reward system and their rescue by BLT-like pulses, a proper diurnal rodent had to be selected and the manifestations of the phenotype noted. A diurnal animal was important as stated before since it would bypass hindrances that occur secondarily to aversive responses that nocturnal animals might have to light. The utilization of diurnal animals is a newer approach that reports short-day affective responses (Ashkenazy-frolinger et al., 2010; Ashkenazy et al., 2009).

Despite the fact that the study conducted in chapter 2 was not conceived as a SAD model (due to the measures taken), it closely resembled one. Hence, framing some of its results as a SAD model is helpful in its analysis. In general, for any animal model to be considered valid, three criteria had to be met (Willner, 1997): (1) face validity, reasonable outward representation of the disorder in behavioral phenotype and symptomatology; (2) construct validity, the same underlying mechanisms or etiology to the human disorder (Willner, 1997); and (3) predictive validity, a similar treatment effectiveness as in the human population of interest. No ideal SAD model has yet been declared (Workman and Nelson, 2011). Our results and those of previous studies will be discussed next, in the context of the criteria, as establishing the credibility of this model is paramount to any conclusions about experiments involving light with these subjects.

Arvicanthis ansorgei in **chapter 2** presented a phase shift in locomotor activity secondary to exposure to a winter-like photoperiod, consistent with previous studies (Leach et al., 2013 a,b) The circadian misalignment secondary to shorter day length and diminished light intensity found in chapter 2 was phase advancement, while in humans with SAD, phase usually delays (Lewy et al., 2006). Phase-shifted circadian locomotor activity patterns in previous experiments had also resulted from exposing *Arvicanthis* species to shortened day length (Leach et al., 2013), even using alternative ways to shorten the day (e.g. not the one used here of shifting “lights off” 2 hours earlier and “lights on” 2 hours later). The phase shifts reported in these previous experiments were also unexpectedly phase advances (Leach et al., 2013). Indeed, even the phase shift hypothesis stated in the introduction is part of the construct validity of SAD models (Lewy et al., 2006). Nevertheless, circadian misalignment in either direction (advancement or delay) is the likely culprit for the emergence of depressive phenotypes evidenced in humans with SAD and SAD animal models (e.g. as measured by sucrose consumption or forced swim tests). Additionally, both humans and these rodents have day

phase preference but the mechanisms by which the preference is attained likely stem from different evolutionary streams (e.g. due to the particular predator-pray relationships of each species).

Locomotor activity rhythms is only one of many behavioral outputs that can be studied. Another two modelling techniques, sucrose consumption and forced swim tests, have been previously used in SAD-modeling studies as a markers of disturbed affect (Workman and Nelson, 2011). Both of these tests are part of the established feasibility of a model with respect to face validity. Previous studies on *Arvicanthis niloticus* (a species closely related to *A. ansorgei*) found diminished sucrose consumption after exposure to light-dark cycles featuring diminished daylight intensity (Leach et al., 2013), and a similar tendency (though not significant) in response to shortened day length (Leach et al., 2013b). In both studies, the forced swim tests also found a significant correlation of increased immobility time, the main outcome of forced swim test indicating more altered mood. Though the data was unpublished, these two tests were conducted in our study as well. A tendency towards desperate behavior was found under winter-like lighting conditions which resolved partially with the light pulses. Additionally, sucrose consumption tests uncovered a day-night pattern reminiscent of a core symptom of SAD known as carbohydrate craving (Møller, 1992). Carbohydrate craving is an intense desire to consume starchy or sugary food, in the late afternoon or early evening after the sun has gone down (Berman et al., 1993; Lewy et al., 2006). *Arvicanthis ansorgei* in LD12:12 displayed higher sucrose intake during the daytime and this pattern changed to more nighttime consumption when subjects were exposed to LD8:16, a pattern ameliorated by BLT-like pulses, both in early and late day.

Administration of light pulses as a rescue mechanism (e.g. BLT) and its outcomes also present crucial timing constraints. The importance of BLT is highlighted in its role as the gold standard of treatment for SAD in humans. Previous human studies have examined optimal time of BLT administration (Lewy et al., 2006), and both evening and morning BLT have shown effectiveness, though best results were found with morning BLT. The hypothetical therapeutic mechanism of BLT in SAD is reduction of the shifted phase (Lewy et al., 2006). Exposure to a light stimulus produces results in accordance with the human phase response curve (Khalsa et al., 2003), so that exposure to light in late day or early night produces a phase delay, and exposure to light in the early day or late night produces phase advance (Duffy and Czeisler, 1985). Thus, in humans, morning BLT effectiveness may be due to amelioration of the phase delay. The BLT-like regimens of **chapter 2** were administered either with “lights on” (early day) or soon before “lights off” (late day) to test the effectiveness of both timings (Mahoney et al., 2001). Interestingly, the phase shift resulting from exposure to winter-like photoperiods is corrected by late-day light pulses but not by early-morning light pulses. While the correction of the phase shift by late-day light pulses may fit the phase shift hypothesis of SAD (and serving as construct validity were it to be treated as a SAD model), it is likely that there is a interplay of the direct and indirect pathways for the effects of light on DAergic activity that explain the physiotherapeutic mechanism of BLT (LeGates et al., 2013; Vandewalle et al., 2011, 2010).

The findings here listed might have consequences in the understanding of SAD treatment. Namely, actigraphy might have a role in monitoring disease progression and BLT treatment response, specially when coupled with light monitoring throughout the day. Indeed, the correction of the locomotor activity phase shift by light late in the day (but not early in the day) might explain why BLT in humans may be therapeutic. Careful study of the circadian features of a subject at a given time in their disease

progression might be crucial for determining optimal treatment, following along with patient-centered focus for current treatments. Similar to how humans usually do not exhibit all diagnostic criteria of a disease, it is unlikely that any single animal model will present all symptoms of a disorder but rather modelling a variety of characteristics of SAD may be useful, depending on research priorities. The difficulties encountered in modelling all of these factors may lead to advocate for multi-pronged approaches utilizing a diversity of reproductively responsive and nonresponsive, diurnal and nocturnal rodents for the investigation of photoperiod-influenced affective responses.

b. Pathways linking light and mood in the indirect pathway

First indications of the indirect pathway by which light affects mood by influencing circadian rhythms were highlighted by the phase shift hypothesis of Seasonal Affective Disorder (SAD) and the hypothetical mechanism by which light therapy regimens ameliorates this condition (Eastman et al., 1998; Lieverse et al., 2011; Riemersma-van der Lek et al., 2008; Terman et al., 1998; Wirz-Justice et al., 2004). Circadian rhythms photoentrained by retinal projections to the SCN are hypothesized to be disrupted by exposure to winter photoperiodic conditions (Lam and Levitan, 2000). In humans, seasonal (winter) depression has been associated with alterations in clock genes (Albrecht 2017, Partonen et al. 2007). One such clock gene, *Per2*, has decreased expression in the SCN *Per2* in mice showing depressive-like behaviors (Logan et al. 2015) and mice with *Per2* mutations are resistant to depressive-like behavior (evaluated in the FST) due to higher brain DA release (Hampp et al. 2008). Hence, clock gene expression was a good starting point to test the indirect pathway by which light signals, via their effect on the circadian clock (read: SCN), induce changes on mood. In **chapter 2**, day–night expression of *Per2*, but not *Avp* or *Bmal1*, in the SCN is affected in *Arvicanthis* exposed to winter-like conditions. However, it is possible that the down regulation at daytime is the consequence of a phase shift rather that an inhibitory effect of photoperiod on *Per2* gene expression since there was a significant phase-advance of daily rhythms in *Arvicanthis* exposed to winter-like conditions. Indeed, in mice with depressive-like behavior the daily rhythm of *Per2* expression in the NAcc and SCN is also phase shifted (Logan et al. 2015).

That said, these changes are a good starting point for establishing that light signals induce changes in the SCN and, in turn, indirect output projections from the SCN influence monoaminergic nuclei (e.g., raphe nuclei [DRN], ventral tegmental area [VTA]) believed to be involved in the generation of depressive phenotypes related to circadian disruption (see figure 5 of chapter 4) (Colwel, 2015). Alternatively, these influences may also come about by the influence of direct projections from ipRGCs to reward-related areas, such as the lateral habenula and the periacqueductal gray area, or even directly to the dorsal raphe nucleus (DRN) (see figure 3 in the introduction) (Hattar et al., 2006; Schmidt et al., 2011).

The idea that light disrupts monoaminergic systems is not new: long term light deprivation had been previously found to damage rats serotoninergic and dopamineric systems and induces depression-like behavior (Gonzalez and Aston-Jones, 2008). Dietary manipulations of the precursors of key neurotransmitters disrupt affective processes in people with SAD, suggesting an underlying vulnerability in people with the disorder (Neumeister et al., 2001). This was true both for tryptophan, the precursor of serotonin (5-hydroytriptamine, 5-HT) (Lam and Levitan, 2000) and tyrosine, the precursor for dopamine (DA) (Cawley et al., 2013). In the following paragraphs we will explore the possible sites were these findings can be mediated.

The VTA is a DAergic area that receives input from the SCN (Luo and Aston-Jones, 2009), and is one of the prominent components of the mesolimbic pathway, the best characterized reward circuit in the brain (see figure 1 in this chapter) (Russo and Nestler, 2014). Studies of the involvement of the mesolimbic pathway in mood regulation show that stress in depression activates VTA DA neurons (Nieoullon, 2002; Rada et al., 2003). Medial Preoptic Nucleus (MPON) is a hypothalamic area that relays the SCN to the VTA and is suggested to work in conjunction with the VTA to integrate motivational aspects of sexual behavior and somatomotor responses (Luo and Aston-Jones, 2009). The MPON is sleep-active and its lesions reduce sleep (Luo and Aston-Jones, 2009), further contributing to the hypothesized circadian-related outputs. The SCN-MPON-VTA pathway is likely one of the indirect pathways by which the biochemical changes in dopamine in the nucleus accumbens and dorsal striatum could take effect.

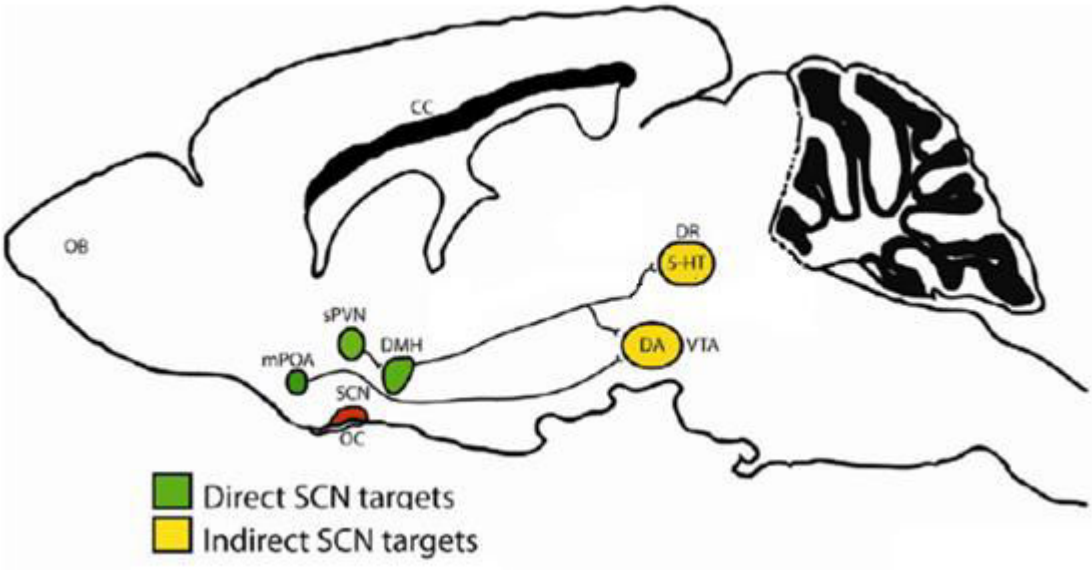

Figure 1. The circadian system regulates multiple monoaminergic brain regions that control mood, and motivated behaviors through indirect connections originating from the suprachiasmatic nucleus (SCN). The SCN projects monosynaptically to multiple hypothalamic nuclei (in green) which subsequently communicate with regions (in yellow) that synthesize dopamine (DA) and serotonin (5-HT). As a result, DA and 5-HT all have a circadian rhythm in their release. (mPOA, medial Preoptic Area; sPVN, subparaventricular nucleus; DMH, dorsomedial hypothalamus; DMH, dorsomedial hypothalamus; VTA, ventral tegmental area; DR, dorsal raphe). Taken from (Colwel, 2015).

The dorsal striatum and nucleus accumbens are two targets of the mesolimbic pathway from the VTA. The features of these areas are being reformulated taking into account circadian properties (Berridge and Kringelbach, 2015; Robbins and Everitt, 1996). Rhythmic changes in dopamine production, transport, reuptake, and metabolism likely create the circadianity within this system (Castaneda et al., 2004; Owasoyo et al., 1979; Paulson and Robinson, 1994; Sleipness et al., 2006). DA tone in both areas is implicated in a variety of circadian behaviors that are disrupted in SAD, such as feeding, sleep–wake cycles and locomotion (Lam and Levitan, 2000; Lewy et al., 2006). Close circadian control of DA signaling in both areas stretches through various levels, likely contributing to the abnormal behavior (Dzirasa et al., 2010). For instance, DA receptor expression has been shown

to rhythmically control expression of circadian genes of the nucleus accumbens, a function that suggest its involvement in mediating drug responses (Akhisaroglu et al., 2005). Studies of reward in the nucleus accumbens show that its activity is consistently reduced in major depression (Drevets et al., 1992; Mayberg et al., 2000). The activity reduction is thought to reflect the diminished reward function behind anhedonia.

In **chapter 2**, dopaminergic neurotransmission was assayed in the dorsal striatum and nucleus accumbens via ratios of DOPAC (3,4-Dihydroxyphenylacetic acid , the main DA metabolite) and DA, measured using High Performance Liquid Chromatography. DOPAC/DA ratios measure the DA turnover and an estimation of dopaminergic neuronal activity even used in pathological conditions, so that higher turnover indicates higher activity (Lathja and Vizi, 2008). Higher DA turnover was found at night (ZT19) than day under LD12:12 conditions, the day-night differences blunted by winter-like LD8:16 conditions. Similarly, in *Arvicanthis niloticus*, the number of hypothalamic DA neurons of animals housed in short photoperiod is downregulated (Deats et al., 2015). In accordance with animal data, several studies reported changes in the DAergic system secondary to SAD or even due to seasons in healthy people, such as greater presynaptic dopamine synthesis and storage (Eisenberg et al., 2011; Hartikainen et al., 1991). All together, these findings agree with previous findings that implied the DA system to be affected by changes in daytime length and light intensity (Abilio et al., 1999).

Beyond its effect on the brain circadian system, light exposure has proven effects on DAergic structures in both humans (Diehl et al., 1994) and animals (Abilio et al., 1999). In an experiment on women with mild seasonal mood changes, an interventions wherein DA synthesis, is selectively reduced by dietary tyrosine and phenylalanine depletion resulted in acute mood disturbances (Cawley et al., 2013). These disturbances ameliorated with light exposure, suggesting that DA changes induced by light may be partly necessary for the beneficial effects of light on mood (Cawley et al., 2013). In **chapter 2**, daily light therapy resolved behavioral and DOPAC/DA disturbances elicited by winter-like conditions as expected. Light effects on DAergic activity may be accounted by a number of changes on the pathway, including modulation of DA transporters activity (Neumeister et al., 2001).

Since DA is not the only neurotransmitter involved in the mesolimbic pathway, reward in the nucleus accumbens may also be incited by DA-independent mechanisms. Opiates activate DAergic transmission in the nucleus accumbens via actions in the VTA, but also directly activate μ-opioid receptors on nucleus accumbens neurons (Castro and Berridge, 2014; Peciña and Berridge, 2013). Opiate projections from the peri-aqueductal gray area are found in the nucleus accumbens (Omelchenko and Sesack, 2010), which has a circadian rhythm of its own and correlates with depression-like behavior when altered (Landgraf et al., 2016). Phase shifts may mediate biochemical changes in this system, which might also be disentrained in SAD. Specific connections from ipRGCs to the peri-aqueductal gray have also been ascertained in mice, which probably mediate these circadian rhythms (Hattar et al., 2006; Schmidt et al., 2011). Stimulation of the nucleus accumbens with opioid-agonists microinjections can double the hedonic impact of sucrose, resulting in higher positive affect change (Peciña and Berridge, 2013). Future studies may include characterizing peri-aqueductal gray transmission as part of the influences on the reward system.

5-HT is another monoaminergic system which we were not able to address due to technical limitations and that should be studied in the future. Selective 5-HT reuptake inhibitors are the pharmacologic gold standards for treatment of depression and also reduce symptoms of SAD, further

implicating monoamines in SAD (Ruhrmann et al., 1998). In previous studies, relapses were noted in SAD patients in remission due to summertime or light therapy when they ate a tryptophan-depleted diet. Additional supportive evidence of the 5-HT claim to relevance in SAD is the finding that carbohydrate consumption increases plasma tryptophan, which might make the evening carbohydrate craving of SAD into a form of self-medication (Møller, 1992).

There are also efferent connections to the 5-HTergic Dorsal Raphe Nuclei (DRN) from the SCN via a relay through the Dorsomedial Hypothalamic Nuclei (DMH) (Monti et al., 2008). The retina also projects directly to the DMH (de Pontes et al., 2010; Morin, 2013), and the DMH displays its own circadian characteristics (de Pontes et al., 2010) and is a critical hub for circadian rhythms (Gooley et al., 2006). Light information from the retina is theorized to act on 5-HTergic neurons in these nuclei, as a recent experiment in gerbils showed photostimulation with low-frequency light reduces c-Fos expression in the DRN during the light phase of an artificial light/dark cycle (de Pontes et al., 2010). Both pathways are involved in photoperiod-responsive affective behaviors (Green et al., 2015). Reciprocally, light-induced phase shifts are attenuated or blocked by 5-HT agonists (de Pontes et al., 2010). A previous study investigated how serotonin levels change in key areas for mood and circadian rhythms (e.g. SCN, cingulate cortex) in response to changing light intensity and revealed significant differences secondary to exposure to dim light (Leach et al., 2013).

All relays centers utilized in these projections are involved in the management of arousal and sleep. As it has been long known that the SCN is the main circadian pacemaker and it is photoentrainable, the hypothesis of the indirect pathway for the effects of light on mood might well be mediated by these pathways. Further experiments are needed to understand the apparent influence of time of day on mood-related behaviors and the possible role of the circadian system.

II. Study of the direct pathway of the reward effects of light

Activation of the reward circuitry with changes in light intensity (LeGates et al., 2013; Vandewalle et al., 2011, 2010) and non-image forming effects of light in different modalities guide the elucidation of the effects of light on mood (Boivin et al., 1996; Cajochen et al., 2000; Dijk et al., 1991). Initial studies of the immediate effects of light on behavior in humans found non-image-forming effects that were evident in imaging, such as increased alertness and vigilance performance in response to light (Badia et al., 1991).

These effects are due to ipRGC projections to the thalamic regions to which these functions correspond (Vandewalle et al., 2009). Similarly ambient light potentially influences reward via its action on the amygdala (Vandewalle et al., 2011, 2010). In a study performed in healthy humans, blue (relative to green) light increased functional connectivity between the amygdala, sensory areas and hypothalamus for emotional processing (Vandewalle et al., 2010). In SAD as well, blue light increased responses to emotional stimuli in the posterior hypothalamus and other regions involved in depression and reward, such as the DRN (Vandewalle et al., 2011). On the other hand, several studies demonstrate acute effects of environmental light intensity on the evaluation of affect elicited by stimuli on healthy subjects but have been confined to laboratory settings (Revell et al., 2006; Vandewalle et al., 2011, 2010). Even the light intensity of stimuli used in such experiments has an effect on affect evaluations: brighter versions of neutral pictures are more positively evaluated than darker versions of the same pictures (Lakens et al., 2013). However, as these were imaging studies, the context was confined to the laboratory.

Only few studies addressed the effect of light intensity on mood ratings in naturalistic environments (aan het Rot et al., 2008b; Dumont and Beaulieu, 2007). Though studies outside of the laboratory environment do not have the possibility of assessing activity of brain areas they are effective ways of achieving real-time measurements. Real-time measurements are crucial for ascertaining the direct effects of light on mood. Following, a new methodology for assessing the effects of light on mood outside the laboratory will be introduced.

a. A new methodology to assess direct effects of light on mood in humans

In **chapter 3 and 4**, a study modality known as experience sampling (aan het Rot et al., 2008) was used to repeatedly assess subjective affect using two outputs of the reward system: wanting and liking (Berridge et al., 2009). Wanting and Liking have been studied in detail in context of reward system dysfunctions, e.g. depression, eating disorders, and drug dependency (Berridge et al., 2009). In this thesis, liking and wanting were evaluated using 6 questions each, addressing different sensory and motivational categories, to be answered on a visual analog scale (based on Born et al., 2011). The study in **chapter 3** comprised a proof-of-concept for combining ambulatory monitoring of environmental light exposure with experience sampling of subjective affect. The method proved feasible and sensitive, and was used again in **chapter 4** to evaluate diurnal mood patterns and light sensitivity of subjective liking and wanting in insomnia (discussed in the next section) though it can also be used for a number of other reward system pathologies (Berridge et al., 2009; Der-Avakian and Markou, 2012; Koob and Volkow, 2010; Parekh and McClung, 2016; Stoffers et al., 2014, 2012; Van Someren et al., 2015; Wassing et al., 2016).

The results of **chapter 3 and 4** indicated that the light intensity has an effect on subjective liking and wanting in young healthy participants and elderly people suffering from insomnia, an effect that seems to be additive to mood ratings circadianity (Byrne and Murray, 2017; Murray et al., 2009). The effect of light intensity was true even when accounting for diurnal rhythms of liking and wanting that were found in the studies of chapter 3 and 4 as well as in past studies (Byrne and Murray, 2017).

b. Direct effects of light on mood in insomnia, and a word on aging

In the healthy young participants of **chapter 3** a correlation of ambient light intensity and subjective affect was found which was not found in the healthy elderly participants in chapter 4. With advanced age, a tendency towards decreased photoreceptor sensitivity, pupil miosis, and yellowing of the lens is noted (Daneault et al., 2016), which is likely central to the aforementioned discrepancy. Age-related changes might reduce the effectiveness of light signaling by ipRGC projections. These changes have also been shown in imaging studies wherein young subjects present higher responses to light than older subjects in important areas for arousal regulation like the thalamus and the VTA and regions involved in reward regulation like the amygdala or the lateral habenula (Daneault et al., 2016; Gruber et al., 2007; Hikosaka, 2010). Other non-image-forming effects of light also show declination with age, e.g. alertness and sleepiness (Daneault et al., 2016). The SCN manifests altered clock genes and neuropeptide expression in old age (Daneault et al., 2016). The aforementioned biochemical alterations may result in the characteristic deficient photoentrainment and desynchronization found in old age. Finally, participants with insomnia seemed to be ever more dependent on light to maintain affect than the healthy controls. This dependence on an environmental factor suggests that a discussion of the pathophysiological framework of hyperarousal seems to be a relevant point of view to take in the next section.

b.1 Role of light in hyperarousal: a pathophysiological framework for depression and insomnia

The pathophysiological framework of hyperarousal is a summation of evidence on several levels that affirms insomnia emerges as part of a round-the-clock state of subjective and objective excitability, defined as increased somatic, cognitive, and cortical activation (Levenson et al., 2015; Riemann et al., 2010). In laymen terms, hyperarousal describes an impaired capacity to detach from the environment. The emergence of the hyperarousal framework has prompted the introduction of pathophysiological characteristics such as circadian and endocrine disturbances into explanations for insomnia. Thus, insomnia is being re-conceptualized from a purely psychological disorder into a psychobiological one (Riemann et al., 2010).

The role of non-image-forming effects of light in the hyperarousal framework has come into inquiry due to the success of light therapy as treatment for insomnia (Shirani and St. Louis, 2009). A metanalysis of light therapy effectiveness in diverse sleep disorders found it a suitable treatment of sleep problems in general, with highest effect for primary insomnia (Maanen et al., 2016). In the metanalysis, a moderator effect of light intensity was also reported exclusively for insomnia (Maanen et al., 2016), which is also a minor hint that light dispensed in other forms (i.e. not in a light therapy-specific format) might have rewarding effects.

The results of **chapter 4** wherein elderly participants with insomnia presented wanting and liking that correlates with ambient light levels mimics the results found in the young participants in **chapter 3**. On the other hand, healthy elderly participants break this correlation and present subjective wanting and liking that are fully independent of ambient light levels. Is there an environmental dependence for reward in healthy youth that "naturally" weans in healthy old age? The permanence of environment-dependence seems to be conducive (or at least correlated) with insomnia and might be a manifestation of the hyperarousal pathophysiological history.

The correlation between ambient light and affect found in insomnia could very well be manifestations of failures to disengage from sensory cues. The amygdala and orbitofrontal cortex (OFC) are two areas that integrate input from different sensory modalities (i.e. sensory cues) with higher order neocortical processing and lower order somatic and emotional functions of the limbic structures (Altena et al., 2010; Genzel et al., 2015; Joo et al., 2013; Winkelman et al., 2013). Both areas show alterations in insomnia and disturbed emotion, stress and reward regulation (Baglioni et al., 2010; Bonnet and Arand, 2010; Colombo et al., 2016; Riemann et al., 2010; Stoffers et al., 2014). For example, imaging studies have found associations between gray matter volume of the OFC and insomnia severity in populations with insomnia, the ability to maintain or resume sleep in the morning in people without sleep complaints (Stoffers et al., 2012; Weber et al., 2013) and with sleep fragmentation in elderly people (Lim et al., 2016; Riemann et al., 2010; Wassing et al., 2016).

Future imaging studies may inquire about the responses of the OFC and amygdala to differing ambient light levels. Such experiments may elucidate the mechanisms by which light has direct influences on mood in health and in the development of hyperarousal. Alternatively, delving into the pathophysiology of insomnia and depression might require large-scale inventories of sleep and wakefulness variables in healthy individuals. A broad range of other domains (e.g. sociology, personality theory, etc.) will be helpful to elucidate the natural course of this environmental engagement found in youth and what characteristics are correlated with its natural weaning in healthy old age. Besides its treatment value, affective response to ambient light and sleep disturbances may

have a prognostic meaning in predicting mental well-being, emotional reactivity, adaptation to negative affect and the evolution of these disorders.

III. Future research

Our results underlined the role of light in disease, and hinted at a fundamental role of light in health. However, the implications of specific baseline effects of light and its absence, whether via modification of its availability (e.g. winter, shift work, utilization of electronic screens, modern lighting) or the capacity to perceive it (e.g. aging), though confirmed, are to be researched further. This field holds many promising lines of research that are extremely relevant to our increasingly-unified world in which globalized forces (e.g. international commerce and service) have caught up with daylight as the main timekeeping signal. Several reasons will determine that light will become a growing concern. International economics will demand services being supplied at all times of day and night or for specific populations to constantly travel between time zones, global warming will determine that the arctic circle will feature a growing population, and if humanity continues on its path of engagement with space exploration circadian rhythms of other planets will definitely be of relevance.

To understand further mechanisms how the processes described arise by the interaction of the enumerated brain areas in health and deviate in disease, visualization will be key. Human imaging techniques are improving and will be a cornerstone of scientific research in the future. Animal models are also likely to continue having utmost importance. Invasive techniques performed on animal models are an ethical and efficient way to make up for the event-related resolution that is missing in human imaging, and it is unlikely that it will ever be replaced, despite the limitations that they also present (Microdialysis, optogenetics, imaging). Additionally, genetic manipulations will continue to be a relevant tool in determining the role of different molecules in the development of SAD under winter photoperiods.

The ever-increasing technological prowess of humankind spells advantages for data science. Promising devices are being introduced, such as smartphones (which are the main input for social media), wristwatch computers (with activity monitors and even temperature), Google Glass (a computer in regular eyeglasses, can potentially record what we are seeing and even pupillary responses), etc. These devices could potentially be integrated as physiological monitors and provide a wealth of variables to integrate and build a clearer picture of how our brains and bodies work, without the limitations of a laboratory environment. This includes tying in the context of ambient light.

Laboratory environments will continue to be relevant due to the heightened temporal and spatial resolution techniques utilized in lab-based investigations of brain areas activity, real time measurements of blood hormone levels, and minute tapering of pharmacological interventions. Combining these elements could create paradigms for exploring how to maximize performance in various modalities that involve the restorative and creative prowess that sleep and dreams involve, including athletics and musicianship. For instance, a prospective study could be designed to monitor feeding, training and sleeping habits of promising young athletes before they accomplish major athletic milestones. This approach would probably eliminate biases (e.g. survivorship bias) in determining factors that influence success in the respective field.

Other future studies might circumvent each limitation in this dissertation. For example, investigating susceptibilities (gender-based, genetic or otherwise) of individual *Arvicanthis ansorgei* exposed to winter-like photoperiods to determine which subject develops a worse depressive phenotype (rather than averaging them out) could provide key insights. The biochemistry of depression may be elucidated by investigating the 5-HTergic and opioidergic systems as well as the DAergic reward system. This might include functional imaging studies in animals, circumventing limitations of invasive techniques (e.g. multiple microdialysis might prove bulky). On the other hand, future human studies might be performed long-term in individuals whose jobs entail shift work (e.g. physicians) to determine whether the direct effects of light on mood can be further dissociated from those mediated by circadian rhythms. Individual susceptibilities, whether age-related or not, might be assessed to elucidate their impact on each the effects of light on mood for each individual.

IV. Conclusions

Along the elaboration of this dissertation, a few of the links in the chain of knowledge that connects light and mood have been revealed. Namely, it has been established that light does indeed have immediate and circadianity-mediated effects on mood and motivational states of populations of two different species. Moreover, the impact of these effects varies with age and other susceptibilities (e.g. insomnia). Additionally, low light levels that correlate with depressive symptoms are in turn correlated with changes in dopaminergic targets, even when these are resolved by treatment with light therapy. Some islands of knowledge are yet to emerge from uncertainty. One such island is how aging intercedes in the development of disturbed affects, and another is the interplay of the other neurotransmitter systems in the pathophysiology of both insomnia and SAD. As science is a continued effort, the findings here reported will surely be built upon to elaborate on these questions.

Overall, the results posted across the chapters in this dissertation indicate that light will most likely see the role of light evolve as a crucial aspect to everyday life. Additionally, its role as treatment will also be found more encompassing, especially as an adjuvant to pharmacotherapy, in an ever-broader range of pathologies (e.g. it might have utility with regards to eating habits, obsessions-compulsions, anxiety, ludopathy, etc.). As such, even healthy laymen may come to see light therapy as an integral part of life, and hence how to dispense a light therapy regime may well become a useful piece of information.

Light interventions could be used as simple treatments to improve cognition, sleepiness, mood, and sleep in normal and pathological aging. For instance, the excessive sleepiness in Alzheimer's and Parkinson's disease, has been associated with increased functional and cognitive impairment (Daneault et al., 2016). However, clear light exposure guidelines for treatment of other disorders have not yet been established (van Maanen, Oort 2015). Light exposure has a positive effect on sleep and mood in these diseases (Daneault et al., 2016) and results here shown imply that light even has a role in mood in healthy young adults. The basic template of light therapy for SAD could serve as a guideline. It consists of a morning dose of 5000 lux/h, usually disposed as 10,000 lux for 30 min, or 2500 lux for 2 h (Daneault et al., 2016). Additional adjustments will most likely be made according to measures such as those done here as well.

Finally, as sunlight plays a crucial of the survival of species on earth, it makes sense that the functioning of human bodies and minds is closely intertwined with the normal patterns of availability of light. The introduction of artificial lighting had led mankind to believe that the influence of daylight

patterns could be overcome. However, research into the role of light in other diseases suggests that our connection to such patterns runs deeper than we imagined. The clinical disorders in which the rewarding effects of light therapy can be capitalized on are likely to expand. Practical application of light therapy would also be aided by efforts to educate clinicians concerning the scientific basis of rewarding effects of light and its clinical applications. The awareness of the effects that light might be having on human physiology serve as a reminder of how frail these processes are, and might encourage closer attention to be paid to other processes which might have been deprioritized in the evolution of science.

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Summary

Reward effects of light

The year 1984 was marked by the publication of the seminal report by Rosenthal and collaborators, in which Seasonal Affective Disorder (SAD) was described and treated with the first controlled trial of bright light therapy (BLT). BLT involves exposing a light to the eyes with appropriate of adequate intensity, duration and time of day; and has been recognized by its effects on the physical and affective symptoms of depression, on sleep time and on sleep duration. These findings promoted further research regarding the modulation of homeostatic processes such as alertness, sleep and body temperature with light. The effects of BLT are produced by mechanisms that do not depend on cortical visual pathways. In 2000, a new opsin was identified that is not present in cones or rods. The opsin, called Melanopsin, allows select cells in the innermost layer of mammalian retinas to be photosensitive, granting them the name intrinsically photosensitive Retinal Ganglion Cells (ipRGC). ipRGCs project to many brain regions, including the main circadian clock, the Suprachiasmatic Nucleus (SCN), where they contribute to circadian photoentrainment; the amygdala where they are involved in in pain, fear and anxiety circuits; and the lateral habenula where they modulate affect and reward.

BLT can modulate the SCN and other targets, such as the dopaminergic reward system, to regulate mood and motivation. The modulation of mood can be accomplished by the effects of light on circadian rhythms (as dictated by the SCN) or by direct pathways between the ipRGCs and reward-related areas. Most studies of BLT have focused on the parameters that influence treatment response such as light intensity and wavelength, duration and timing of exposure; but few have studied the mechanisms by which light induces a rewarding effect. As a result, the role light in human well-being has not been understood, as well as the pathophysiological mechanisms that relate light in SAD.

In this project, a framework was proposed to elucidate the rewarding effects of light and the behavioral and biochemical mechanisms by which they come to effect. This effort is multidimensional, and two experimental approaches have been adopted here: (1) a diurnal animal model for the study of effects of light on the behavior and biochemical responses to a photoperiod change (equatorial to winter) and their recovery using pulses of light; and (2) a human model to study the influence of light on the mood of healthy participants and insomniacs (a pathology showing motivational deficits). This last modality had a particular emphasis on creating experimental and control conditions, with the use of environmental sampling, which ensured a blind study.

The first approach used was an animal model using the diurnal rodent *Arvicanthis ansorgei*. In this experiment, subjects were exposed to a control photoperiod consisting of a standard light-dark

cycle LD12:12h (150 lux of light during the day, lights-on at 7:00 [defined as Zeitgeber time 0, ZT0] and lights-off at 19:00 [defined as ZT12]; with <5 lux during the remaining night) for three weeks. Then, the subjects passed through a winter photoperiod consisting of a LD8:16h cycle (lights-on at 9:00 [redefined as ZT0] and lights-off at 17:00 [ZT8]) with a light intensity reduced to 45 lux during the day and for 6 weeks. Furthermore, 2 cohorts of these subjects also received BLT-like hour-long pulses of light (approx. 1900 lux) either early or late in the day. The locomotor activity was recorded throughout the experiment. The dopamine release was assayed in the dorsal striatum and nucleus accumbens at two different time points to demonstrate the daily response of this new photoperiod and compare it with equivalent samples obtained from control subjects (in equatorial photoperiod). Additionally, the expression in the suprachiasmatic nucleus (SCN) of clock genes *Per2* and *Bmal1*, as well as the output peptide *Avp* was also assayed to distinguish day-night differences in their expression in the aforementioned conditions.

The results of this series of experiments indicated that the combination of shortening day-length with diminished daylight intensity induces a phase change of locomotor activity rhythms in *Arvicanthis ansorgei*. This effect induces increased locomotion during the night. Dopamine content by high performance liquid chromatography was evaluated in two structures of the reward system of the brain: the dorsal striatum and the nucleus accumbens. Under control conditions, daily rhythmicity of dopamine turnover could be demonstrated with higher levels at ZT19 (night) compared to ZT7 (day). This particular rhythmicity was lost under winter photoperiodic conditions. Additionally, *Per2*, but not *Bmal1* or *Avp*, revealed altered expression in winter-like photoperiods.

The variations in day and night measures of dopamine turnover and *Per2* expression ameliorated by both light pulses. However, the circadian locomotor activity rhythms which were advanced due to the LD8:16h photoperiods were delayed (returned closer to the normal LD12:12h levels) with exposure to the late day pulses but remained advanced with exposure to early day pulses. These results show how light can affect the reward system and behaviors associated.

A second study modality aimed at elucidating the immediate effects of light on affect in humans in everyday life in their natural environment. Experience sampling was used to assess affect repeatedly and complemented by simultaneous ambulatory recording of natural fluctuations in ambient light. Subjective affect was measured using two variables: Liking, the actual pleasure component of reward that can be dissociated from the eliciting stimuli; and Wanting, the association of a stimulus with a specific reward. These measures have been studied in detail in context of reward system dysfunctions, eg. depression, eating disorders, and drug dependency. Liking and Wanting

were evaluated using 6 questions each, addressing different sensory and motivational categories, to be answered on a visual analog scale.

Using smartphones, participants were probed by alarms to answer the questions 8 times per day across semi-randomized intervals. Ambient light intensity was simultaneously assessed continuously with an ambulatory recorder worn as a brooch on the chest. Mixed effect models were used to assess how Wanting and Liking varied during the day in accordance to the intensity of exposed ambient light within the 30 minutes prior to the assessment.

In the first study on 27 healthy volunteers, 1102 valid time-point assessments showed that time of day significantly modulates Wanting and Liking, resulting in a peak at 17:49 and 18:50, respectively. Higher Wanting and Liking scores were found after exposer to more intense light. More traditional positive mood (e.g. happy, relaxed, efficient) and negative mood (e.g. anxious, tense, sad) questions showed little sensitivity to light intensity.

In the second study, 1764 valid time point assessments were obtained in 17 participants with insomnia and 18 healthy volunteers. Compared to those without sleep disorders, participants with insomnia showed lower ratings of Wanting and Liking. Higher light intensities partly ameliorated the overall lower subjective Liking but not Wanting in participants suffering from insomnia. There were no significant changes in wanting and liking from interactions of light intensity with insomnia severity or duration of insomnia. Other measures of positive or negative mood were not significantly affected by interactions of Insomnia with light intensity.

The results show that Wanting and Liking are diurnally modulated. Moreover, they increase with prior light intensity both in young adults and aged participants with insomnia, but not in aged participants without sleep disorders, who consistently gave markedly high ratings. The results of this study suggest that insomniacs have a deficit in feeling, recognizing or reporting subjective affect. The deficit may in part be restored by bright environmental light, which has to be confirmed in experimental studies.

Samenvating

Belonende effecten van licht

Het jaar 1984 werd gekenmerkt door de publicatie van het baanbrekende rapport van Rosenthal *et al.*, waarin Seasonal Affective Disorder (SAD) werd beschreven en felle licht therapie (FLT) voor het eerst werd toegepast in een gecontroleerde trial. FLT in kort, is het blootstellen van licht aan de ogen met voldoende intensiteit, duur, op een specifiek tijdstip van de dag; en is gekenmerkt bij de effecten op de fysieke en affectieve symptomen van depressie, op slaaptijd, en op slaapduur. Deze bevindingen bevorderden verder onderzoek naar de modulatie van licht op homeostatische processen zoals alertheid, slaap, en lichaamstemperatuur. De effecten van FLT worden geproduceerd door mechanismen die niet afhankelijk zijn van corticale-visuele circuits. In 2000 werd een nieuw 'opsin' geïdentificeerd die niet aanwezig is in kegels of staven. De opsin, Melanopsin genaamd, maakt het mogelijk dat specifieke cellen in de binnenste laag van retina van zoogdieren lichtgevoelig zijn, waardoor ze de naam 'intrinsiek lichtgevoelige Retinale Ganglioncellen' (ipRGC) hebben gekregen. ipRGC's heben projecties naar vele hersenregio's, waaronder de belangrijkste circadiane klok, de Suprachiasmatic Nucleus (SCN), waar ze bijdragen aan de circadiane photoentrainment; de amygdala waar ze betrokken zijn bij pijn-, angst- en stresscircuits; en de laterale habenula waar ze affect en beloning moduleren.

FLT kan de SCN en andere hersengebieden moduleren, zoals het dopaminerge beloningssysteem om de stemming en motivatie te reguleren. De modulatie van licht op stemming kan worden bereikt door de effecten op circadiane ritmen (gedirigeerd door de SCN) of door directe paden tussen de ipRGC's en beloning-gerelateerde gebieden. De meeste studies naar FLT hebben zich gericht op de parameters die de respons van de behandeling beïnvloeden, zoals de lichtintensiteit en golflengte, de duur, en de timing van de blootstelling; maar enkelen hebben de mechanismen bestudeerd waarmee licht een belonend effect induceert. Hierdoor is de rol dat licht speelt in het menselijk welzijn nog niet begrepen, en in het bijzonder is zijn de pathofysiologische mechanismen die SAD induceren nog onbekend.

In dit project werden de belonende effecten van licht bestudeerd door de gedrags- en biochemische mechanismen waarmee ze tot stand komen te verduidelijken. Dit project is multidimensionaal en er zijn twee experimentele benaderingen gekozen: (1) een dagdier-model werd gebruikt voor de studie naar de effecten van licht waarbij specifiek werd gekeken naar de gedrags- en biochemische respons op een fotoperiodieke veranderingen (equatoriaal tot winter) en het herstel met lichtpulsen; en (2) een menselijk model om de invloed van licht op de stemming van gezonde deelnemers en slapelozen te bestuderen (een pathologie die motivatieprobelemen vertoont). Deze laatste modaliteit had een

bijzondere nadruk op het creëren van experimentele en controle-omstandigheden met het gebruik van environmental-sampling, waardoor de studie blind was voor de onderzoeker.

De eerste gebruikte benadering was een diermodel voor de studie van gedrags- en biochemische veranderingen naar winterachtige fotoperiodes met een diurnaal knaagdier, *Arvicanthis ansorgei*. In dit experiment werden de dieren gedurende drie weken blootgesteld aan een controle foto-periode bestaande uit een standaard licht-donkercyclus LD12:12 uur (150 lux licht gedurende de dag, licht aan om 7:00 [gedefinieerd als Zeitgeber tijd 0, ZT0] en licht- uit om 19:00 [gedefinieerd als ZT12], met <5 lux gedurende de resterende nacht). Vervolgens gingen de dieren gedurende 6 weken door een winter-fotoperiode bestaande uit een LD8: 16h cyclus (licht aan om 9:00 [opnieuw gedefinieerd als ZT0] en licht uit om 17:00 [ZT8]) met een lichtintensiteit verlaagd tot 45 lux gedurende de dag. Bovendien ontvingen 2 cohorten van deze dieren ook FLT-achtige lichtpulsen van een uur aan het begin of het einde van de dag (ongeveer 1900 lux). De locomotorische activiteit werd gedurende het hele experiment geregistreerd. De dopamineafgifte in het dorsale striatum en de nucleus accumbens werd getest op twee verschillende tijdstippen om de dagelijkse respons van deze nieuwe fotoperiode aan te tonen en te vergelijken met equivalente monsters verkregen van controle-dieren (in equatoriale fotoperiode). Bovendien werd de expressie in de SC) van klokgenen *Per2* en *Bmall*, evenals het uitgangspeptide Vasopresin (*Avp*) ook getest om dag-nacht verschillen in hun expressie in de hiervoor genoemde omstandigheden te onderscheiden.

De resultaten van deze reeks experimenten gaven aan dat de combinatie van verkorte daglengte en verminderde daglichtintensiteit een faseverandering induceert in de motoriek-ritmes in *Arvicanthis ansorgei*. Dit effect veroorzaakt een verhoogde motoriek tijdens de nacht. Het dopaminegehalte werd geëvalueerd in twee structuren van het beloningssysteem van de hersenen met 'high performance liquid chromatography': het dorsale striatum en de nucleus accumbens. Onder controle condities kon de dagelijkse ritmiciteit van de dopamine-turnover worden aangetoond, met hogere niveaus bij ZT19 (nacht) in vergelijking met ZT7 (dag). Deze specifieke ritmiciteit ging verloren onder de winter-fotoperiodieke omstandigheden. Bovendien onthulde *Per2*, maar niet *Bmal1* of *Avp*, veranderde expressie in winterachtige fotoperiodes.

De variaties van dag en nacht dopamine-turnover en *Per2* expressie werden ook op vergelijkbare wijze verbeterd door beide lichtpulsen. De circadiane motoriek-ritmes die waren opgeschoven als gevolg van de LD8:16 uur fotoperiodes werden echter vertraagd (teruggekeerd naar de LD12: 12h toestand) met blootstelling aan lichtpulsen op het einde van de dag, maar bleven opgeschoven na blootstelling aan lichtpulsen aan het begin van de dag. Deze resultaten laten zien hoe licht het beloningssysteem en de daarmee samenhangende gedragingen kan beïnvloeden.

Een tweede studiemodaliteit was gericht op het bestuderen van de directe effecten van licht op emotionele stemming bij mensen in het dagelijks leven in hun natuurlijke omgeving. Ervaringssteekproeven werden gebruikt om de emotionele stemming herhaaldelijk te meten en deze metingen werden aangevuld door gelijktijdige ambulante registratie van natuurlijke fluctuaties in omgevingslicht. Subjectieve stemming werd gemeten met twee variabelen: 'Liking', de pleziercomponent van de beloning die kan worden losgemaakt in response van een opwekkende stimulus; en 'Wanting', de associatie van een stimulus met een specifieke beloning. Deze variabelen zijn in detail bestudeerd in verband met verstoringen in het beloningssysteem, bijv. in depressie, eetstoornissen en drugsverslaving. Liking en Wanting werden geëvalueerd met elk 6 vragen die verschillende sensorische en motiverende categorieën uitvragen. Antwoorden worden gegeven op een visuele analoge schaal. Met behulp van smartphones werden de deelnemers 8 keer per dag (over semi-willekeurige intervallen) herinnerd om vragen te beantwoorden. De intensiteit van het omgevingslicht werd tegelijkertijd continu gemeten met een ambulante sensor die werd gedragen als een broche op de borst. Mixex-effects modellen werden gebruikt om de variabiliteit in Wanting en Liking gedurende de dag te associeren aan de intensiteit van het omgevingslicht, 30 minuten voorafgaand aan de observatie.

In het eerste onderzoek met 27 gezonde vrijwilligers, toonden 1102 geldige tijdpunt-observaties aan dat Wanting en Linking aanzienlijk worden gemoduleerd door het tijdstip van de dag, met een piek in Wanting en Liking om respectievelijk 17:49 en 18:50 uur. Hogere scores voor Wanting en Liking werden gevonden na blootstelling aan intens licht. De traditionele positieve stemmingsmaten (bijv. blij, ontspannen, efficiënt) en negatieve stemmingsmaten (bijv. angstig, gespannen, verdrietig) vertoonden weinig gevoeligheid voor lichtintensiteit.

In de tweede studie werden 1764 geldige tijdpunt-observaties verkregen bij 17 deelnemers met slapeloosheid en 18 gezonde vrijwilligers. In vergelijking met mensen zonder slaapstoornissen, vertoonden deelnemers met slapeloosheid lagere scores op Wanting en Liking. Bloodstelling aan hogere lichtintensiteit verbeterde gedeeltelijk de algemene lage subjectieve Liking, maar niet Wanting, bij deelnemers met slapeloosheid. Er waren geen significante veranderingen in Wanting en Liking in relatie tot interacties tussen lichtintensiteit en de ernst van slapeloosheid of de duur van slapeloosheid. Andere maten van positieve of negatieve stemming werden niet significant beïnvloed door interacties tussen slapeloosheid en lichtintensiteit.

De resultaten laten een diurnale modulatie van Wanting and Liking zien. Bovendien nemen deze maten toe met toenemende lichtintensiteit, zowel bij jonge volwassenen als bij oudere deelnemers met slapeloosheid, maar niet bij oudere deelnemers zonder slaapstoornissen die consequent opvallend

hoge scores gaven. De resultaten van deze studie suggereren dat slapelozen moeite hebben met het voelen, herkennen of rapporteren van subjectieve stemming. Dit kan mogelijk gedeeltelijk worden hersteld door bloodstelling aan fel omgevingslicht, wat in experimentele studies moet worden bevestigd.

Résumé

Effets récompensants de la lumière

L'année 1984 a été marquée par la publication du rapport séminal de Rosenthal et ses collègues, qui définit le Trouble Affectif Saisonnier (TAS) et présente le premier essai contrôlé de la luminothérapie (LT). Cette thérapie, qui consiste à exposer sur les yeux une lumière d'une intensité et d'une durée adéquate/appropriée, aux moments les plus favorables/opportuns de la journée, a été reconnue pour ses effets sur les symptômes affectifs et physiques de la dépression, le temps d'endormissement et la durée du sommeil. Ces résultats favorisent de nouvelles recherches sur la capacité de la lumière à moduler les processus homéostatiques tels que la vigilance, le sommeil et la température corporelle.

Les effets de la LT sont produits par des mécanismes qui ne dépendent pas des voies visuelles corticales. En 2000, une nouvelle opsine qui n'apparaît ni dans les cônes ni dans les bâtonnets a été identifiée. Ce récepteur couplé à la protéine G, appelé Mélanopsine, se trouve dans 1 à 2% des cellules ganglionnaires, situées dans la couche cellulaire la plus interne de la rétine, chez les mammifères. De ce fait, ces cellules ont été nommées Cellules Ganglionnaires de la Rétine intrinsèquement photosensibles (ipRGC). Les ipRGCs projettent à de nombreuses régions encéphaliques, incluant l'horloge principale, le Noyau Suprachiasmatique (NSC), où elles permettent le photoentraînement circadien mais également dans l'amygdale qui est impliquée dans la douleur, la peur et les circuits de l'anxiété, et dans l'habénula latérale qui participe au système de la récompense.

La LT peut moduler le NSC ou d'autres cibles comme le système dopaminergique, faisant partie du système de la récompense, pour réguler l'humeur et la motivation. La plupart des études concernant la LT ont mis l'accent sur les paramètres qui influencent la réponse au traitement comme l'intensité et la longueur d'onde de la lumière, la durée d'exposition et le moment où elle a lieu mais peu ont étudié l'effet récompensant de la lumière. De ce fait, la façon dont la lumière intervient dans le bien-être des êtres humains est méconnue, et en particulier les mécanismes physiopathologiques qui induisent un TAS.

Dans ce projet, un cadre a été proposé pour élucider les effets récompensants de la lumière et les mécanismes comportementaux et biochimiques par lesquels ils pourraient être entraînés. Cet effort est multidimensionnel, et deux approches expérimentales ont été adoptées ici : (a) un modèle animal diurne pour l'étude de la réponse comportementale et biochimique à un changement de photopériode (d'été à d'hiver) et le sauvetage de ces réponses par créneaux de lumière ; (b) un modèle humain pour étudier l'influence de la lumière sur l'humeur de participants en bonne santé et des insomniaques (une

pathologie montrant des déficits de motivation), avec un accent particulier sur la création d'une combinaison de conditions expérimentales et de contrôles qui assurent une étude en aveugle, avec l'utilisation d'un échantillonnage environnemental.

La première approche utilisée fut le modèle animal avec le rongeur diurne, *Arvicanthis ansorgei*. Dans cette expérience, les sujets ont été exposés à une photopériode contrôle consistant en un cycle standard lumière-obscurité (Light-Dark, LD) 12:12h (une lumière à 150 lux le jour qui s'allume à 7:00 [défini comme le temps Zeitgeber, ZT0] et s'éteint à 19:00 [défini comme le ZT12] pendant trois semaines). Puis les animaux sont passés dans une photopériode hivernale consistant en un cycle LD 8:16h (la lumière s'allume à 9:00 [redéfinie comme ZT0] et s'éteint à 17:00 [ZT8]) avec une intensité lumineuse réduite à 45 lux lors du jour et ce, pendant 6 semaines. De plus, deux cohortes de ces animaux a reçu un régime de LT pendant 4 semaines consistent de un créneau de lumière de 1 heure (150 lux), sois une heure avant que la lumière s'éteigne (ZT7) ou une heure au début du l'allumage (ZT0). L'activité locomotrice a été enregistrée tout au long de l'expérience. Le contenu de dopamine a été dosée dans le striatum dorsal et le noyau accumbens à deux points horaires différents pour mettre en évidence la réponse journalière de cette nouvelle photopériode et la comparer à des échantillons équivalents obtenus chez des sujets contrôles (sans changement de photopériode). De même, l'expression des gènes d'horloge *Per2* et *Bmal1*, ainsi que le peptide *Vasopressine (Avp),* ont été également évalué pour déterminer les différences jour-nuit de leur expression dans les conditions susmentionnées.

Les résultats de cette série d'expériences ont indiqué que le raccourcissement de la longueur du jour, ainsi que la diminution de l'intensité lumineuse, induit un changement de phase du rythme de l'activité locomotrice. Cet effet induit une activité locomotrice plus importante pendant la nuit. La quantité de dopamine a été évaluée avec chromatographie liquide du haut performance dans deux structures du système de la récompense du cerveau antérieur : le striatum dorsal et le noyau accumbens. Dans les conditions de contrôle, une rythmicité journalière a pu être mise en évidence avec des niveaux plus élevés à ZT19 (nuit) par rapport à ZT7 (jour) lesquelles sont perdues dans des conditions photopériodiques hivernales. De plus, *Per2*, mais pas *Bmal1* ou *Avp*, ont montré une expression altérée dans les photopériodes de type hivernal.

Les variations jour-nuit de la dopamine et expression de *Per2* ont été améliorés par les créneaux de lumière le début de matin (ZT0) et à la fin du jour (ZT7). Cependant, les rythmes journalières de l'activité locomotrice qui ont été avancés en raison des photopériodes LD8:16h ont été retardés (retournés à l'état LD12:12h) avec une exposition a la lumière uniquement à ZT7. Ces résultats

montrent comment la lumière, d'une manière dépendante du temps, peut affecter le système circadien, le système dopaminergique et les comportements associés.

La seconde modalité d'étude a été d'étudier les effets de la lumière sur le comportement affectif chez l'Homme dans son milieu naturel. Les études concernant les effets de la lumière sont limitées par les difficultés à créer des conditions de contrôle par rapport à l'exposition à la lumière en conditions expérimentales. Deux expériences ont été menées utilisant une combinaison d'échantillonnage de ressentis au cours de la journée ainsi que des capteurs portables mesurant la luminosité. Ces expériences ont permis d'évaluer les effets des fluctuations lumineuses environnementales sur l'affect subjectif du sujet en dehors d'un laboratoire. Les participants ont subi une méthode d'échantillonnage de ressenti avec des smartphones afin d'évaluer subjectivement les mesures de « liking », la composante réelle de plaisir de la récompense qui peut être dissociée de stimuli gratifiants, et le « wanting », l'association d'un stimulus à une récompense spécifique. Ces mesures ont été étudiées en détail dans le contexte d'un dysfonctionnement du circuit de la récompense, allant de la dépression, la récompense alimentaire, à la récompense des drogues. Les participants ont répondu aux questions avec des échelles visuelles analogiques 8 fois par jour pendant sept jours. L'intensité lumineuse a été évaluée en continu avec un enregistreur ambulatoire porté comme broche sur la poitrine. Les modèles d'effets mixtes ont été utilisés pour évaluer la façon dont le « wanting » et le « liking » ont varié au cours de la journée et de l'intensité d'exposition à la lumière dans les minutes précédant l'évaluation. Afin de mener à bien cette séparation, des modèles à effets mixtes ont été utilisés afin de tenir compte de la variabilité en intégrant des fonctions sinus et cosinus de l'heure du jour dans la construction des modèles qui représentent l'effet de la lumière sur l'affect subjectif.

Dans une première expérience, 27 volontaires en bonne santé 1102 évaluations ont indiqué que le temps de la journée module significativement le wanting, ce qui entraîne un pic à 17h49 et aussi le liking avec un pic a 18h50. Le liking et le wanting augmentent avec l'augmentation de l'intensité de la lumière. Cet effet n'a pas été expliqué par les différences individuelles moyennes d'intensité lumineuse auxquelles ont été exposés les personnes au cours de la semaine d'enregistrement mais plutôt par la fluctuation de la lumière. Les autres mesures d'humeur positives et négatives n'ont pas montré de corrélation significative avec l'intensité lumineuse

Dans la deuxième expérience, 17 participants souffrant d'insomnie et 18 volontaires sains ont également été évalués sur 1764 évaluations. Par rapport à ceux sans troubles du sommeil, les participants souffrant d'insomnie ont montré des notations plus faibles du wanting et du liking. Des intensités lumineuses plus élevées ont en partie amélioré le liking subjectif inférieur, mais non le

wanting chez les participants souffrant d'insomnie. Il n'y avait pas de changements significatifs dans le liking et wanting avec interactions de l'intensité lumineuse et la sévérité de l'insomnie ou la durée de l'insomnie. Les autres mesures d'humeur positive ou négative n'ont pas été significativement affectées par les interactions de l'insomnie avec l'intensité lumineuse.

Les résultats montrent que l'heure du jour module à la fois le Wanting et le Liking. Il y’a un déficit global en matière d'évaluation hédonique chez les insomniaques par rapport aux témoins. Les participants sans troubles du sommeil sont restés à des niveaux élevés de wanting et liking indépendamment de l'intensité de la lumière. De plus, cet effet ne pouvait pas être expliqué par des disparités dans les niveaux d'exposition à la lumière entre les groupes. Les résultats de notre étude suggèrent que les insomniaques présentent un déficit en affect subjectif sensible à la lumière, où l'exposition à celle-ci apporte une faible amélioration mais néanmoins significative.

De plus amples études devraient être menées afin d'élucider l'effet des signaux lumineux ambiants sur les circuits de récompense et comment ces effets changent dynamiquement avec l'âge. La lumière peut avoir un rôle dans la réduction de la qualité de vie des insomniaques, qui est comparable à celle des maladies chroniques telles que l'insuffisance cardiaque congestive et le trouble dépressif majeur. La promesse de la luminothérapie comme une modalité de traitement pour l'insomnie semble avoir une base solide à cet égard. D'autres traitements comportementaux incluent la régulation du sommeil, des thérapies de relaxation et le contrôle des stimulations qui se sont révélés être bénéfiques; et pour poursuivre dans la même lignée, il ne peut qu'être conseillé de suivre des horaires quotidiens réguliers à titre préventif.

Résumé

Pour élucider les effets récompensants de la lumière, deux approches expérimentales ont été adoptées. Une étude chez le rongeur diurne *Arvicanthis ansorgei* indique que le raccourcissement de la longueur du jour avec la diminution de l'intensité lumineuse induit des changements du rythme de l'activité locomotrice, de la quantité de dopamine dans le système de la récompense et sur l'expression du gène *Per2* dans le noyau suprachiasmatique. Ces altérations ont été améliorées par l'exposition journalière à des créneaux d'une heure de lumière à la fin du jour. Dans une étude humaine, le bien-être subjectif mesuré par d'échantillonnage de ressentis, a été corrélée avec des mesures de fluctuations lumineuses environnementales chez des participants en bonne santé et des insomniaques. Les résultats ont montré que le bien-être subjectif augmente proportionnellement à l'intensité de la lumière chez de jeunes en bonne santé contrairement à un déficit global en matière d'évaluation hédonique chez les insomniaques. De plus amples études devraient être menées afin d'élucider l'effet des signaux lumineux environnementaux sur les circuits de récompense.

Mots-clefs : Récompense, lumière, humeur, rythme circadien, dépression saisonnière, *Arvicanthis*, dopamine, rongeur diurne

Abstract

To elucidate the reward effects of light, two experimental approaches have been adopted. An experiment for the study of the effects of exposure to a winter-like photoperiod on the diurnal rodent *Arvicanthis ansorgei* indicated that shortened day length with reduced light intensity induces a phase change in locomotor activity, alterations in the dopamine content in reward system structures, and alterations in the *Per2* clock gene expression in the suprachiasmatic nucleus. These measures were improved by daily exposure to a one-hour pulse of light at late in the day. In a human model, subjective wellbeing, measured by experience sampling, was correlated with ambient luminosity measurements in participants with insomnia and healthy controls. Results indicated that subjective wellbeing increases with increasing light intensity in healthy young volunteers, in contrast to an overall deficit in reward evaluation in insomniacs. Light exposure should be taken into account as an important factor in determining the quality of life of insomniacs and in depression. Further studies should be conducted to elucidate the effect of ambient light signals on reward circuits.

Key-words : Reward, light, mood, circadian rhythms, seasonal depression, *Arvicanthis*, dopamine, diurnal rodent

PhD Portfolio

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PhD period: October 2013 – September 2018
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Courses

- Français pour débutants, University of Strasbourg, France 2014
- Cognitive Electrophysiology Methods, University of Amsterdam, Netherlands 2015
- Advanced MR techniques for Neuroscientists, Donders Institute, Netherlands 2015
- Computational approaches to neuroimaging, Donders Institute, Netherlands 2015

Conferences attended

- Understanding the Neural Basis of Diurnality, University of Strasbourg, France 2013
- The Cognitive Thalamus, University of Strasbourg, France 2013
- The Self: From autobiographical memories to the lifestory, University of Strasbourg 2014
- 2nd Neurotime Annual Meeting, Amsterdam, Netherlands 2014
  (Oral Presentation)
- Nervous System Development in Invertebrates, Basel, Switzerland 2015
- 3rd Neurotime Annual Meeting, Basel, Switzerland 2015
  (Oral Presentation)
- 4th Neurotime Annual Meeting, Strasbourg, France 2016
  (Oral Presentation)
- Interdisciplinary Conference on Psychedelics Research, Amsterdam, Netherlands 2016

Publications

Itzhacki J, Clesse D, Goumon Y, Van Someren EJW and Mendoza J. **Light rescues circadian behavior and brain dopamine abnormalities in diurnal rodents exposed to a winter-like photoperiod.** Brain Struct Funct. 2018 Mar 20. doi: 10.1007/s00429-018-1655-8.

Itzhacki J, Te Lindert BHW, van der Meijden WP, Kringelbach ML, Mendoza J & Van Someren EJW. **Environmental light and time of day modulate subjective liking and wanting.** Emotion 2018 Mar 5. doi: 10.1037/emo0000402.

Te Lindert BHW, Itzhacki J, van der Meijden WP, Kringelbach ML, Mendoza J, Van Someren EJW. **Bright environmental light ameliorates deficient subjective 'liking' in insomnia: an experience sampling study.** Sleep 2018 Feb 7. doi: 10.1093/sleep/zsy022.

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Abbreviations

5-HT	Serotonin (5-hydroxytriptamine)
AH	Anterior Hypothalamus
AVP	Arginin-vasopresin (Vasopressin)
BLT	Bright Light Therapy
Bmal1	Brain muscle ARNT-like protein 1 (clock gene)
BST	bed nucleus of the stria terminalis
CAMS	Circadian Activity Monitoring System
CI	Confidence Interval
CP	Caudate-putamen
CS	Circadian Stimulus
DA	Dopamine
DIS	Difficulty Initiating Sleep
DISS	Daytime Insomnia Symptom Scale
DMH	Dorsalmedial Hypotalamic Nucleus
DMS	Difficulty Maintaining Sleep
DOPAC	dihydroxiphenolacetic acid
DRN	Dorsal Raphe Nucleus
EEG	Electroencephalogram
EMA	Early Morning Awakening
ES	Experience Sampling
HH:MM	Hours:Minutes
HPLC	High Performance Liquid Chromatography
ICC	Intraclass correlation
ID	Insomnia Disorder
IGL	Intergeniculate Leaflet
ipRGC	intrinsically photosensitive Retinal Ganglion Cells
ISI	Insomnia Severity Index
LD	light-dark
LD12:12h	12 hours of light and 12 hours of dark
LD8:16h	8 hours of light and 16 hours of dark
LGd	dorsal region of Lateral Geniculate Nucleus
LGy	ventral region of Lateral Geniculate Nucleus
LH	Lateral Hypothalamus
LHb	Lateral Habenula

M+SD	Median and Standard deviation
MA	Medial Amygdala
MCTQ	Munich Chronotype Questionnaire
MPON	Medial Preoptic Nucleus
NAcc	Nucleus Accumbens
NIF	non-image forming
Npas2	Neuronal PAS domain protein 2
OFC	Orbitofrontal Cortex
OPN	olivary pretectal nucleus
PAG	Peri-aqueductal Gray
Per2	Period 2 (clock gene)
PRC	Phase response curve
pSON	peri-supraoptic nucleus
PSQI	Pittsburgh Sleep Quality Index
SAD	Seasonal Affective Disorder
SC	superior colliculus
SCN	Suprachiasmatic Nucleus
SPZ	Subparaventricular zone
TOD	Time of Day
VAS	Visual Analog Scales
VLPO	Ventrolateral Preoptic Nucleus
VTA	Ventral Tegmental Area
ZT	Zeitgeber Time

Jacobo ITZHACKI

Effets récompensants de la lumière

Résumé

Pour élucider les effets récompensants de la lumière, deux approches expérimentales ont été adoptées. Une étude chez le rongeur diurne *Arvicanthis ansorgei* indique que le raccourcissement de la longueur du jour avec la diminution de l'intensité lumineuse induit des changements du rythme de l'activité locomotrice, de la quantité de dopamine dans le système de la récompense et sur l'expression du gène *Per2* dans le noyau suprachiasmatique. Ces altérations ont été améliorées par l'exposition journalière à des créneaux d'une heure de lumière à la fin du jour. Dans une étude humaine, le bien-être subjectif mesuré par d'échantillonnage de ressentis, a été corrélée avec des mesures de fluctuations lumineuses environnementales chez des participants en bonne santé et des insomniaques. Les résultats ont montré que le bien-être subjectif augmente proportionnellement à l'intensité de la lumière chez de jeunes en bonne santé contrairement à un déficit global en matière d'évaluation hédonique chez les insomniaques. De plus amples études devraient être menées afin d'élucider l'effet des signaux lumineux environnementaux sur les circuits de récompense.

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