UNIVERSITY OF LIÈGE
FACULTY OF MEDICINE

Investigating the biological impact of light on brain function using 7T ultra-high field MRI

Islay Campbell

Sleep and Chronobiology Lab, GIGA-CRC In Vivo Imaging
University of Liège
Belgium

Supervisor:
Prof. Gilles Vandewalle

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Biomedical and Pharmaceutical Sciences

Academic year 2023-2024

Investigating the biological impact of light on brain function using 7T ultra-high field MRI

Islay Campbell Master of Sciences, Imperial College London, 2015

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Biomedical and Pharmaceutical Sciences

Supervisor:

Gilles Vandewalle, PhD, Cyclotron Research Centre/Biomedical Sciences Faculty

ULiège Examining Board:

Christine Bastin, PhD, President of the Jury,

Christophe Phillips, PhD, Secretary of the Jury,

Christina Schmidt, PhD,

Steve Majerus, PhD

External Examiners:

Yvonne de Kort, PhD, Eindhoven University of Technology, Netherlands

Nina Milosavljevic, PhD, University of Manchester, UK

UNIVERSITY OF LIÈGE MARCH 2024

Acknowledgements

I would like to thank multiple people who have provided guidance, support, and encouragement during my PhD, without whom this piece of work would not be possible.

Firstly, I would like to thank my supervisor, Gilles Vandewalle, for his continued support. Thank you for allowing me to come to Belgium and complete my PhD at the Cyclotron Research Centre. I'm very grateful for the encouragement and guidance throughout this journey, especially helping to navigate and continue the HILIGHT project during the complicated COVID-19 period. I greatly appreciate the time you dedicated to reading my work and especially, for helping me to calmly complete the final stages of my PhD.

I would also like to extend my gratitude to the members of my jury, Yvonne de Kort, Nina Milosavljevic, Christine Bastin, Steve Majerus, Christina Schmidt, and Christophe Phillips. Thank you for taking the time to read and evaluate my PhD thesis. I appreciate the opportunity to discuss my work with you all later.

To everyone who worked or helped with the HILIGHT project, I would like to say a massive thank you. The HILIGHT project would not have been possible without all your help and continued support. I sincerely appreciate the time and effort you gave to ensure the project succeeded. To begin with I would like to say thank you to those who helped with the initial set up of the project. Thank you to Puneet for helping me master Opensesame, the eye-tracking system and for your support in the protocol set-up. Thank you to Siya, for setting up the HILIGHT MRI sequences and for the help in developing the MRI-compatible light system. To Elise, Ilenia, and Roya your support and endless help with the project has been invaluable. I sincerely appreciate all the work and effort you spent helping with data acquisition. I know data acquisition has not always been easy, but it was much more enjoyable with you all. I would also like to say thank you to Erik and Catherine for the recruitment and data acquisition, your help was appreciated. Also, thank you to the ASLEEP team, Katya, and Nasrin, for your invaluable help in times of need.

I would like to thank Fermin and John, who joined the HILIGHT team a bit later and who have taken over the running of the project. John, your help with the recruitment has been incredible. Fermin, thank you for taking over the running of the project. Finally, thank you to all the master's students who have helped with the data acquisition.

To all my wonderful friends that I have made at the CRC, I would not have been able to achieve this without you. I am incredibly grateful for all of your support, encouragement and help through difficult times. Thank you for the memories and for ensuring the time I spent in Belgium was full of laughter and joy. I will miss all of you and I wish you all the best for the future.

To my parents, thank you for all the love and support and for ensuring I didn't give up on pursuing my PhD. To JJ and Alexis, thank you for encouraging and supporting me from afar. I can't wait to see you and baby Cass very soon! To my wee sister Izzy, thank you for supporting me through the final months of my PhD. I would not have made it without you.

I am incredibly grateful to everyone who has helped me over the last four years. Thank you for helping me successfully complete my PhD.

Abstract

Lighting environments can influence our health and wellbeing with several health issues being associated with aberrant lighting. The human retina detects light through two different pathways, the classical visual system, which is required for visual formation, and the non-image forming (NIF) system, which detects environmental irradiance. The NIF system is maximally sensitive to the shorter blue wavelength visible light (~480nm) and mediates light influence on several circadian, neuroendocrine, and neurobehavioral functions. Electrical lighting environments have evolved over the decades with the development of incandescent and fluorescent lighting and now on to the increasingly more energy-efficient light-emitting diode (LED) bulbs. The change in electrical lighting has also come with a change in the emission spectrum of our indoor light environments, which are becoming more blue-light heavy due to common 'white' LEDs being a blue-enriched light source with a peak around 440–460 nm.

Knowledge of the NIF system coupled with advancements in LEDs led to the emerging idea of integrative lighting. Integrative lighting would consider the visual acuity and biological effects of light. To ensure integrative lighting benefits human health and wellbeing and doesn't exacerbate light misuse, fundamental questions about how light influences cognitive and emotional functioning need to be addressed.

The cortical circuitry underlying light's stimulating impact is not established in humans. To gain a deeper understanding of how the NIF impact of blue-enriched light may influence the subcortical areas of the brain, we utilised two techniques, ultra-high-field 7 Tesla (7T) functional magnetic resonance imaging (fMRI) and infrared eye tracking equipment. Young healthy adults completed an fMRI protocol with simultaneous eye tracking whilst exposed to the light of various illuminance and engaged in auditory cognitive tasks.

In my thesis, we first aimed to characterise the task-evoked pupil response (TEPR) associated with auditory inputs under different light levels. The analysis showed that even with a smaller sustained pupil size during brighter light blocks, a higher light level triggers a stronger TEPR to auditory stimulation. We presume this is through the recruitment of the locus coeruleus, a brainstem region that may be involved in some of light's NIF functions.

Secondly, we analysed if there were regional differences in light illuminance across the human hypothalamus whilst engaged in cognitive tasks. The findings reveal that there were distinct response dynamics to increasing illuminance across the hypothalamus. Specifically, higher illuminance triggered an increase in activity over the posterior part of the hypothalamus and the opposite was observed in the anterior and ventral parts of the hypothalamus. The nuclei comprising the posterior part of the hypothalamus may be among the key initial sites of the stimulating impact of light on human cognition and alertness, putatively through orexin and histamine signalling.

Thirdly, we analysed if there were regional differences in illuminance across the human amygdala whilst engaged in an emotional task. The findings reveal that there were distinct response dynamics to increasing illuminance across the amygdala. We found that the medial

nucleus and other medial/superior parts of the amygdala show a marked reduction of activity under higher illuminance when processing emotionally charged stimuli. These findings provide additional insight into the mechanisms that may underlie the benefits of light therapy.

Overall, the thesis highlights part of the brain circuitry underlying the impact of blue-enriched light on (cognitive) brain functions. The work emphasises that a better understanding of how light impacts cognitive and emotional functioning will help to achieve integrative light solutions to benefit health and wellbeing in the future.

Résumé

L’environnement lumineux peut influencer notre santé et notre bien-être, avec plusieurs problèmes de santé associés à un éclairage inapproprié. La rétine détecte la lumière par deux voies différentes : le système visuel classique, nécessaire à la formation d'image, et le « système sans formation d'image » (NIF), qui détecte l'irradiance. Le système NIF est plus sensible aux longueurs d'ondes bleues plus courtes de la lumière visible (~480nm) et exerce une influence sur plusieurs fonctions circadiennes, neuroendocriniennes et neurocomportementales. L'éclairage électrique a évolué au fil des décennies avec le développement de l'éclairage incandescent et fluorescent et maintenant des ampoules à diodes électroluminescentes (LED) de plus en plus économes en énergie. L'évolution de l'éclairage électrique s'est également accompagnée de modifications du spectre d'émission lumineux intérieur, qui devient plus riche en lumière bleue, car les LED "blanches" courantes sont des sources de lumière enrichies en bleu dont le pic se situe autour de 440-460 nm.

La connaissance du système NIF et les progrès réalisés dans le domaine des diodes électroluminescentes ont conduit à l'émergence de l'idée d'éclairage intégratif. L'éclairage intégratif prendrait en compte les aspects visuels et les effets émotionnels et biologiques de la lumière. Pour s'assurer que l'éclairage intégratif est bénéfique pour la santé et le bien-être de l'être humain et qu'il n'exacerbe pas l'utilisation inappropriée de la lumière, il convient de répondre à des questions fondamentales sur l'influence de la lumière sur le fonctionnement cognitif et émotionnel.

Les circuits corticaux qui sous-tendent l'impact stimulant de la lumière ne sont pas totalement établis chez l'être humain. Pour mieux comprendre comment l'impact NIF de la lumière bleue peut influencer les zones sous-corticales du cerveau, nous avons utilisé deux techniques, l'imagerie par résonance magnétique fonctionnelle (IRMf) 7 Tesla (7T) à très haut champ et un équipement de suivi oculaire à infrarouge. De jeunes adultes en bonne santé ont suivi un protocole d'IRMf avec un suivi oculaire simultané pendant qu'ils étaient exposés à une lumière de différentes intensités et qu'ils effectuaient des tâches cognitives auditives.

Durant mon travail de thèse, nous avons d'abord cherché à caractériser la réponse pupillaire évoquée par une tâche (TEPR) associée à des stimulations auditives sous différents niveaux de lumière. L'analyse a montré que même si la taille de la pupille est plus petite pendant les périodes de lumière plus brillante, un niveau de lumière plus élevé déclenche une TEPR plus forte. Nous supposons que cela est dû au recrutement du locus coeruleus, une région du tronc cérébral qui est peut-être impliquée dans certaines des fonctions NIF de la lumière.

Nous avons ensuite analysé s'il existait des différences régionales de l’impact de la lumière dans l'hypothalamus lors de l'exécution de tâches cognitives. Les résultats révèlent une dynamique de réponse distincte dans l'hypothalamus en fonction de l'éclairage. Plus précisément, un éclairage lumineux plus élevé déclenche une augmentation de l'activité dans la partie postérieure de l'hypothalamus et l'inverse est observé dans les parties antérieure et ventrale de l'hypothalamus. Les noyaux comprenant la partie postérieure de l'hypothalamus pourraient être parmi les sites initiaux clés de l'impact stimulant de la lumière sur la cognition et la vigilance humaines, potentiellement par le biais de l'orexine et de l'histamine.

Nous avons enfin analysé s'il existait des différences régionales de l’impact de la lumière dans l'amygdale lors d'une tâche cognitive et émotionnelle. Les résultats révèlent une dynamique de réponse distincte dans l'hypothalamus en fonction de l'éclairage dans l'amygdale. Nous avons constaté que le noyau médian et d'autres parties médianes/supérieures de l'amygdale présentent une réduction marquée de l'activité en cas d'augmentation de l'éclairage lors du traitement de stimuli chargés émotionnellement. Ces résultats pourraient permettre de mieux comprendre les mécanismes qui peuvent être à l'origine des bienfaits de la luminothérapie.

Dans l'ensemble, mon travail de thèse met en évidence une partie des circuits cérébraux qui sous-tendent l'impact de la lumière bleue sur les fonctions cérébrales (cognitives). Le travail met en avant qu'une meilleure compréhension de l'impact de la lumière sur le fonctionnement cognitif et émotionnel contribuera à la mise en place de solutions lumineuses intégratives au bénéfice de la santé et du bien-être.

Table of Contents

List of Figures

List of Tables

Abbreviations

AAA	Anterior amygdaloid area
ANTs	Advanced Normalization Tools
ATA	amygdala transition areas
BEL	Blue Enriched Light
BLH	Blue Light Hazard
BOLD	Blood-Oxygen-Level-Dependent
CCT	Correlated Colour Temperature
CIE	Commission internationale de l'éclairage
DOC	Disorders of Consciousness
EEG	Electroencephalogram
EWN	Edinger–Westphal Nucleus
fMRI	functional Magnetic Resonance Imaging
GABA	γ-aminobutyric acid
GLM	General Linear Model
GLMM	Generalised Linear Mixed Models
GRE-EPI	Gradient-Recalled Echo-Planar Imaging
IGL	Intergeniculate leaflet
ipRGCs	Intrinsically Photosensitive Retinal Ganglion Cells
FWE	Family-wise Error
LC	Locus Coeruleus
LEDs	Light- Emitting Diodes
LGN	Lateral Geniculate Nucleus
LH	Lateral hypothalamus
NA	Noradrenaline
NIF	Non-Image Forming
MB	Mamillary Bodies
Mel-EDI	Melanopic Equivalent Daytime Illuminance
MNI	Montreal Neurological Institute
MP2RAGE	Magnetization-Prepared with 2 RApid Gradient Echoes
mPFC	medial prefrontal cortex
MRI	Magnetic Resonance Imaging
OPN	Olivary Pretectal Nuclei
PET	Positron Emission Tomography
PLR	Pupil Light Reflex
PON	Preoptic Nucleus
QC	Quality Control
RGCs	Retinal Ganglion Cells
RF	Radio Frequency
RTs	Reaction Times
S-cones	Short Wavelength-Cones
SAD	Seasonal Associative Disorder
SC	superior colliculus
SCN	Suprachiasmatic Nucleus
SD	Standard Deviations
TEPR	Task-Evoked Pupil Response
TMN	Tuberomammillary Nucleus
VLPO	Ventrolateral Preoptic Nucleus
vmPFC	Ventromedial Prefrontal Cortex
UHF	Ultra-High Field

Main Scientific Contribution

Oral conference presentations as first author

Campbell, I., Sharifpour, R., Paparella, I., Beckers, E., Balda Aizpurua, J. F., Mortazavi, N., Berger, A., Talwar, P., Koshmanova, E., Lamalle, L., Philips, C., Sherif, S., Vandewalle, G. **"Exposure to light modulates emotional brain responses in the hypothalamus."**2022. SLTBR. Manchester, United Kingdom

Campbell, I., Beckers, E., Sharifpour, R., Paparella, I., Balda Aizpurua, J. F., Berger, A., Koshmanova, E., Mortazavi, N., Lamalle, L., Sherif, S., Vandewalle, G. **"Characterising the pupil response under different light conditions during a functional MRI protocol**." 2022. ESRS. Athens, Greece.

Publications as first author

Campbell, I., Sharifpour, R., & Vandewalle, G. (2023). **Light as a Modulator of Non-Image-Forming Brain Functions—Positive and Negative Impacts of Increasing Light Availability.** *Clocks and Sleep, 5*(1), 116-140. doi:10.3390/clockssleep5010012

Campbell, I., Beckers, E., Sharifpour, R., Berger, A., Paparella, I., Balda Aizpurua, J. F., Koshmanova, E., Mortazavi, N., Sherif, S., & Vandewalle, G. (2023). **Impact of light on task-evoked pupil responses during cognitive tasks.** *Journal of Sleep Research e14101.* https://doi.org/10.1111/jsr.14101

Campbell, I., Sharifpour, R., Balda Aizpurua, J. F., Beckers, E., Paparella, I., Berger, A., Koshmanova, E., Mortazavi, N., Read, J., Zubkov, M., Talwar, P., Collette, F., Sherif, S., Philips, C., Lamalle, L., & Vandewalle, G. (2023). **Regional response to light illuminance across the human hypothalamus.** *bioRxiv* (2023). doi:10.1101/2023.12.19.572317.

Campbell, I., Balda Aizpurua, J. F., Sharifpour, R., Paparella, I., Beckers, E., Mortazavi, N., Berger, A., Koshmanova, E., Read, J., Zubkov, M., Talwar, P., Collette, F., Sherif, S., Philips, C., Lamalle, L., & Vandewalle, G. (2023). **Exposure to light modulates the activity of the medial amygdala during emotional processing.** *Under preparation.*

Chapter 1

General Introduction

Chapter from our published review:

Campbell, I., Sharifpour, R., & Vandewalle, G. (2023). **Light as a Modulator of Non-Image-Forming Brain Functions—Positive and Negative Impacts of Increasing Light Availability**. *Clocks and Sleep, 5*(1), 116-140. doi:10.3390/clockssleep5010012

General Introduction

There are two light-sensitive photoreceptor pathways in the human retina. First, the classical visual system is required for image formation and relies on rod and cone photoreceptors. Second, the non-image forming (NIF) system, also referred to as the "nonvisual" system, detects environmental irradiance (Lucas et al., 2014; Wässle, 2004). The main photoreceptor of the NIF system was discovered only about two decades ago, termed intrinsically photosensitive retinal ganglion cells (ipRGCs) due to the expression of the photopigment melanopsin, which is maximally sensitive to blue-wavelength light around 480 nm (Berson et al., 2002; Lucas et al., 2014; Provencio et al., 2000). Melanopsin expressing ipRGCs mediate the influence of light on several circadian, neuroendocrine, and neurobehavioral functions collectively defined as NIF, i.e., functions not directly related to image formation. Light can have acute impacts on NIF functions including melatonin suppression, pupillary constriction, and stimulation of alertness and cognitive performance (Brainard et al., 2001; Gooley et al., 2012; Vandewalle, Maquet, et al., 2009). On a longer timescale, light can affect circadian entrainment and influence mood (Legates et al., 2012; Wirz-Justice et al., 2020).

Light is now emerging as being central to our health and wellbeing, and several health issues have been associated with aberrant light environments including sleepiness, cognitive impairments, mood, and sleep disorders (Boyce, 2022; Wirz-Justice et al., 2020). The development of light-emitting diode (LED) lighting was a major technological advance that was awarded the 2014 Nobel Prize for Physics (Von Dollen et al., 2014) and has turned light into a truly tuneable parameter. However, with LEDs being easily incorporated into many devices, light use has expanded. Moreover, many commonly used white LEDs are relatively rich in blue-wavelength light (C. Zhang et al., 2023).

This narrative literature review discusses the multiple aspects that we think should be considered to predict the impact of modern, changing light environments on brain functions. We include what we think are important and relevant papers to cover the relatively broad topics of this review, but we cannot be exhaustive and are inherently subjective in our selection. We first provide an overview of the retinal and neural light-sensitive pathways and our current understanding of light's effect on cognition, sleep, alertness, and mood. We also discuss the potential biological impacts of increasing LED lighting and take into consideration other questions including lifetime changes from adolescence to senescence, light's impact on mood and emotional regulation, and the confusion surrounding light's impact on the retina.

Current ‘Modern’ Lighting

White LEDs were first developed in 1996 (Von Dollen et al., 2014) but they have been adopted worldwide due to their falling prices, improved lighting qualities, and lower energy consumption. There are different ways to produce white LEDs, but the most common method is by combining a blue LED and yellow phosphors, which absorb part of the blue light to emit longer wavelength photons, producing light that appears white (Pimputkar et al., 2009). These common “white” LEDs are typically blue-enriched light sources with a peak around 440–460 nm, which falls within the sensitivity range of the NIF system, and a second broader peak in the yellow–green wavelength region (**Figure 1-1**-A). This emission spectrum is very different from incandescent and fluorescent lights, which have a dominant wavelength closer to the sensitivity of the classical visual system (550 nm) (Lucas et al., 2014). The advent of incandescent lighting has led to blue-depleted indoor light exposure but the conversion to LED lighting means we are now becoming increasingly exposed to more blue-wavelength light. However, whether this change in the spectral composition of light sources translates to a differential impact on NIF functions is still being determined.

What is known is that light’s impact depends on the timing and duration of the exposure, meaning that more blue-wavelength (~460–480 nm) light can have beneficial or detrimental effects, including changes in alertness and cognition (Gaston et al., 2015; Wirz-Justice et al., 2020). Governments worldwide are adopting policies in favour of LED lighting. Lighting industries are even proposing LED-integrative lighting products to improve health, mood, or wellbeing, often with little solid scientific backing (Houser et al., 2020). LED lighting is now found everywhere in our homes and offices, and LED back-lighted screen displays are now found in computers, televisions, phones, tablets, etc. As detailed in the review, it may not be the spectrum of LEDs but rather the timing of their use that is most problematic. The use of LEDs is expected to continue to rise rapidly worldwide in the coming decades (Pimputkar et al., 2009), making understanding the NIF impact of light a timely research question.

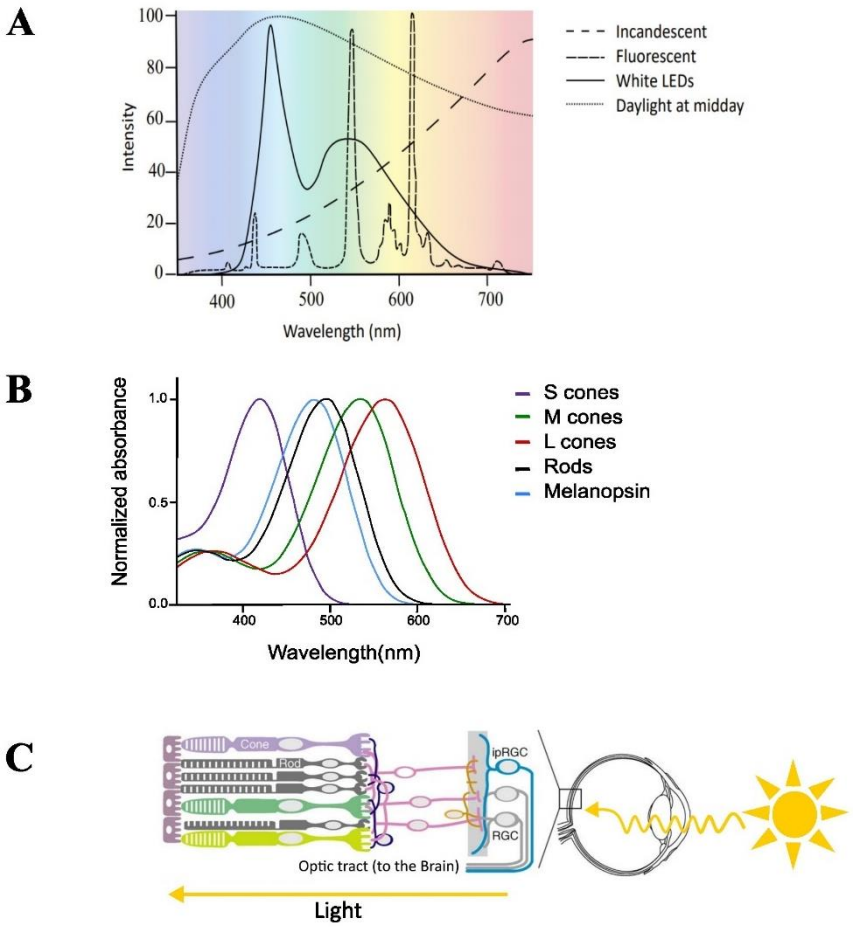


Figure 1-1. Photoreceptor sensitivities and light spectra. (A) Spectrum of white LED, fluorescent, and incandescent light sources and natural daylight. **(B)** Spectral sensitivities of retinal photoreceptors in primates. **(C)** Wiring and position of retinal photoreceptors. ipRGCs: intrinsically photosensitive retinal ganglion cells expressing melanopsin. RGC: retinal ganglion cells. Reproduced and adapted with permission from **(Hatori & Panda, 2010)**.

Classical Light Sensitive Pathways

Rods and cones densely populate the photoreceptor outer layer of the retina. They are sensitive to light due to having specialized stacked membranes that contain high concentrations of photopigments (Wässle, 2004). Rods are required for scotopic night vision as they can detect very low amounts of photons and they express the photopigment rhodopsin, which has a peak sensitivity at 507 nm (Lucas et al., 2014). Scotopic vision is colour-blind as there is only a single type of rod. In humans, photopic vision is mediated by three different cone photoreceptors, each with different peak wavelength sensitivities, enabling colour vision. Short-wavelength cones (S-cones) express opsin cyanolabe and have a peak sensitivity around 420 nm; mid-wavelength cones express chlorolabe opsin and are most sensitive around 535 nm photons; and long wavelength-cones express erythrolabe with a peak sensitivity around 565 nm (peak values may vary slightly depending on pre-retinal filtering). This results in an overall maximal photopic sensitivity over the yellow–green part of the visible light spectrum (~550 nm) (Lucas et al., 2014). Cones are insensitive to scotopic light levels (~10–6 Cd/m2) and rod saturation begins at photopic light levels (~10 Cd/m2). Between scotopic and photopic lies mesoscopic vision with rod and cone contribution to (partially coloured) vision (Stockman & Sharpe, 2006). Following signal processing by amacrine, horizontal and bipolar cells, rods, and cones signal and then reach the retinal ganglion cell (RGC) layer. A large number of RGC types have been isolated with different wavelengths and spatial opponency, which shape their overall axonal response in the optic nerve (Wässle, 2004). Importantly, these RGCs typically respond immediately to light in a time-locked manner. The subcortical brain areas innervated by classical photoreceptors include the thalamic lateral geniculate nucleus (LGN) before reaching occipital areas involved in complex image formation, but also the superior colliculus and the lateral posterior pulvinar complex (DeSimone et al., 2015).

Non-Image Forming System

The prediction of a second novel photoreceptor system within the mammalian eye was first made in 1927 by Keeler, noting that “apparently blind” mice still maintained pupil constriction when exposed to light (Keeler, 1927). This prediction would not be considered seriously until about 50 years later when rodent animal models with complete enucleation were reported to lose a NIF function and photoentrainment could not be explained by the photoreceptors of the classical visual system (Klein & Weller, 1972; J. S. Takahashi et al., 1984). The later development of mouse models genetically engineered to completely lack rods and cones allowed for true testing of Keeler’s prediction. These mouse models exhibited NIF responses to light, such as pineal melatonin suppression, pupillary light reflex, and circadian entrainment, with a maximal sensitivity towards the shorter wavelengths (Freedman et al., 1999; Lucas, 1999; Lucas et al., 2001). Furthermore, the retinal hypothalamic tract remained intact in “rod/coneless” mice, projecting to suprachiasmatic nuclei (SCN), olivary pretectal nuclei (OPN), and inter-geniculate leaflet regions (known to be involved in circadian entrainment and NIF responses) (Provencio, Cooper, et al., 1998).

In humans, Czeisler et al. reported in the 1990s that a completely blind individual retained melatonin suppression by light (Czeisler et al., 1995). Later studies of colour-blind subjects suggested that deficiencies in any of the cone types had no detectable impact on melatonin suppression by light (Ruberg et al., 1996). Two studies further investigated the spectral sensitivity of melatonin suppression in humans with normal sight and these studies identified the shorter wavelength region of the visual spectrum (446–477 nm) as having the greatest impact on melatonin suppression (Brainard et al., 2001; Thapan et al., 2001).

The NIF system was discovered to be mainly driven by melanopsin-expressing ipRGCs, a third class of retinal photoreceptors (Berson et al., 2002; Lucas et al., 2014). Melanopsin was first discovered in batrachian skin right before the turn of the millennium and then later identified in mammalian retinas (Provencio, Jiang, et al., 1998). Melanopsin-expressing ipRGCs only make up around 5% and 1% of all retinal ganglion cells in mouse and human retina, respectively, and these photoreceptors measure environmental irradiance (Lucas et al., 2014). The difference in melanopsin-expressing ipRGCs between mice and humans may be due to different methodologies used, with human ipRGCs studies unable to use the most sensitive techniques. The blue-sensitive melanopsin photopigment is encoded by the OPN4 gene (Provencio et al., 2000). Longer wavelengths, such as red light (>~600 nm), have a largely reduced effect on the photopigment light transducing form. Animal and human studies confirmed that melanopsin is the main photopigment of the NIF system, shifting its sensitivity towards short-wavelength light, around 480 nm (**Figure 1-1**-B) (Brainard et al., 2001; Lucas et al., 2001; Panda et al., 2002; Thapan et al., 2001).

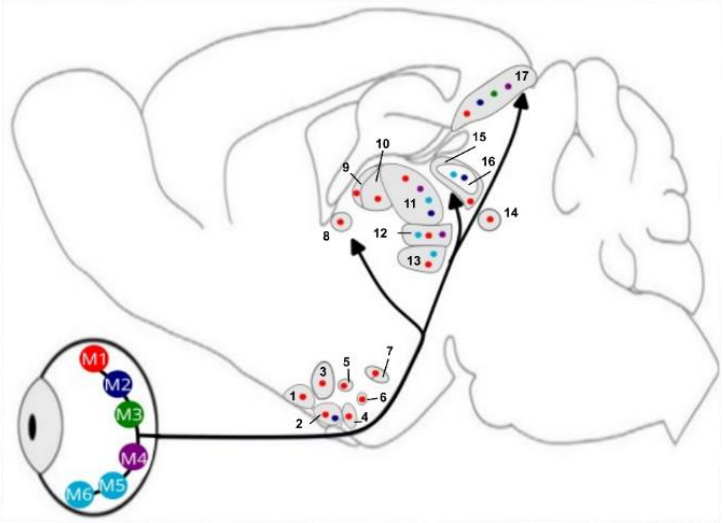
Melanopsin is a dual-state photopigment, meaning it exists in two stable photon absorption states, driving phototransduction and chromophore regeneration, respectively, similar to rhabdomomeric photopigments of invertebrates (Matsuyama et al., 2012; Mure et al., 2007, 2009). This is in contrast to rod and cone photopigments where photons drive the phototransduction while chromophore regeneration requires an enzyme cycle taking place in the nearby cells of the retinal pigment epithelium (Mure et al., 2009). The conversion of melanopsin between its 11-cis and all-trans isoforms is driven by different light wavelengths with 480 nm photons most efficient in the 11-cisto-all-trans switch triggering phototransduction, while the all-trans-to-11-cis reconversion takes place at longer wavelengths, subject to debate (Mure et al., 2007, 2009). Biochemistry investigation reported that chromophore regeneration maximal sensitivity lies only about 10 nm away from the peak of phototransduction efficiency (Matsuyama et al., 2012). In contrast, in vivo studies in mice and humans suggest that orange/reddish wavelength light (590–620 nm) most efficiently drives chromophore regeneration and leads to the subsequent increase in intrinsic photosensitivity of ipRGCs (Mure et al., 2007, 2009). Increased sensitivity following longer wavelength light may depend on the particular in-lab protocol (including periods of complete darkness and different light levels) as studies combining blue (479 nm) and red (627 nm) light LEDs failed to modulate light's impact (Papamichael et al., 2012).

Contrary to the initial predictions, the classical and NIF systems are not separate. Melanopsin-ipRGCs innervate the LGN and, indirectly, the primary visual cortex. They are involved in some important visual functions such as brightness detection, rod/cone light level adaptation (contributing to the remarkable 10^{12} fold change our vision operates over), and they were

reported to contribute to coarse image formation and spatial contrast detection (Allen et al., 2019; Brown et al., 2010, 2012; Ecker et al., 2010). Further roles of melanopsin-ipRGCs contributing to visual functions include improved visual information processing in the retina and dLGN through the modulation of fast narrowband oscillations; maintaining a generalized increase in neural activity in response to changing background light intensity; and increasing the firing rate in the optic nerve due to changes in ambient light level (Milosavljevic et al., 2018; Storchi et al., 2015, 2017).

IpRGCs also receive input from rods and cones, which is required for complete NIF responses (**Figure 1-1**-C) (Güler et al., 2008). For instance, rods and cones contribute to the phasic pupil light reflex (PLR) at continuous and lower light intensities, whereas melanopsin mainly contributes to the PLR at higher light intensities and sustains the PLR for longer durations (Gooley et al., 2012). Importantly, melanopsin-driven photoreception outlasts light exposure from seconds to tens of minutes after lights off. These characteristics of ipRGCs drive so-called post-illumination pupil constriction, an "after-effect" constriction, that offers a unique means to directly measure melanopsin function in humans (Kankipati et al., 2010).

Rodent studies have established that melanopsin ipRGCs are composed of at least six different subtypes (to date: M1–M6) determined based on morphological and functional features. IpRGC subtypes have varying levels of melanopsin expression, complex interactions with rods and cones, and different projection patterns to subcortical brain regions (**Figure 1-2**) (Tri & Do, 2019). M1 ipRGCs are currently the best-defined subtype. They have the highest level of melanopsin photopigment expression and densely innervate the SCN, the site of the master circadian clock (making up 80% of total SCN ipRGC innervation) (Baver et al., 2008). M1 ipRGCs appear to be the main subtype required for encoding environmental irradiance (Zhao et al., 2014). The M1 ipRGCs also project to the OPN, driving the pupil light reflex; the perihabenular zone, involved in mood regulation; the intergeniculate leaflet, involved in the circadian response to light; the lateral hypothalamus, important for sleep and wakefulness regulation; the visual ventral LGN; and other subcortical areas, but with a reduced innervation density (Baver et al., 2008; Tri & Do, 2019). The population of M1-ipRGCs can cover a broad range of light intensities allowing for an efficient response to changes in environmental irradiance (Milner & Do, 2017). Furthermore, using a different genetic labelling technique, ipRGCs were found to project to the central amygdala, zona incerta, and the accessory optic system (Delwig et al., 2016).



IpRGC projections in mice	
1	Preoptic area
2	Suprachiasmatic nucleus
3	Subparaventricular zone
4	Peri-supraoptic nucleus
5	Anterior hypothalamus
6	Lateral hypothalamus
7	Medial amygdala
8	Bed nucleus of the stria terminalis
9	Perihabenular nucleus
10	Lateral habenula
11	Dorsal lateral geniculate nucleus
12	Intergeniculate leaflet
13	Ventral lateral geniculate nucleus
14	Periaqueductal gray
15	Olivary pretectal nucleus shell region
16	Olivary pretectal nucleus core region
17	Superior colliculus

Figure 1-2. Schematic of main ipRGC projections in mice. Adapted with permission from (Hattar et al., 2006; Tri & Do, 2019). Information from (Ecker et al., 2010; Hattar et al., 2006; Tri & Do, 2019; Zhao et al., 2014). Numbers of the scheme correspond to numbers in the adjacent table. Coloured dots correspond to known projection of ipRGCs subtypes in rodents (M1 to M6).

The other ipRGC subtypes are less well-defined. M2 ipRGCs make up the other 20% of the retinal input to the SCN. M2 ipRGCs may also play a role in pupil constriction, as they contribute 55% of ipRGC innervations to the OPN (Baver et al., 2008). Recently, M4 ipRGC subtypes have been implicated in a multi-synaptic pathway involved in mood regulation (L. Huang et al., 2019). Other non-M1 ipRGC subtypes are known to contribute to visual perception (Sonoda & Schmidt, 2016). The exact roles of each subtype in NIF and visual functions are still being elucidated.

Importantly, the melanopsin-driven light response is considered to be sluggish, but this initial observation depends on the ipRGC subtype and light levels. M1 peak responses are detected within a second while M4 peak responses can take up to 20 s (Zhao et al., 2014). When functional rods and cones are present, ipRGCs respond immediately to light (Güler et al., 2008). It is worth mentioning that it is believed that ipRGCs primarily drive NIF functions via the release of excitatory neurotransmitters at NIF brain targets, but there is a subset of ipRGCs in mice that release inhibitory neurotransmitters (GABA), through which some non-image forming behaviours, such as pupillary reflex and circadian entrainment become relatively insensitive at low light levels (Sonoda et al., 2020). There is growing research on human ipRGCs with potentially four ipRGC subtypes identified. However, studies on human ipRGCs are scarce and need to be replicated, and many unanswered questions remain about the differences between mouse ipRGCs and human ipRGCs (see review (Mure, 2021)).

There is evidence of other photoreceptors contributing to the NIF system. S-cone photoreceptors seem to contribute to circadian photoentrainment through a blue–yellow colour discrimination circuit involving M1-ipRGCs. It is proposed that colour opponency evolved to distinguish between the different sky colours encountered at different times of the day, to convey timing information to the SCN and to support correct entrainment (Mouland et al., 2019; Rivera & Huberman, 2020; Walmsley et al., 2015). In mice, there is some evidence that cones also contribute to measuring ambient light irradiance and send signals to the SCN. However, melanopsin's role in measuring light intensity is more significant and makes melanopic irradiance an effective parameter to control the impact of light on the circadian system (Mouland et al., 2021).

In mouse models, ultraviolet-sensitive cones have a role in contributing to circadian entrainment and sleep–wake regulation (Van Oosterhout et al., 2012). S-cones contribute to light-evoked activity in the PON (Pretectal Olivary Nucleus), important for the light pupil reflex, and also seems to facilitate ipRGC response arrest after lights off in rodents (Allen et al., 2011). There is conflicting evidence for the role of S-cones in humans, with one study having found no role for S-cones in NIF neuroendocrine and alerting responses (Spitschan et al., 2019), but a further study has found that S-cones do contribute to melatonin suppression (Brown et al., 2021). This may indicate that the role of S-cones in melatonin suppression depends on the specific characteristics of the light exposure, such as its spectral composition or duration. S-cones may contribute to up to one-third of the response if exposure lasts ~30 min (Brown et al., 2021), while melanopsin photoreception would exclusively drive the response with ~90 min exposure (Spitschan et al., 2019). Overall, there is still a debate about the relative contributions of rods, cones and melanopsin photoreception to the various NIF functions of light. However, ipRGCs are the only cells through which light affects NIF functions. In other words, if ipRGCs are blocked or removed, no NIF impact of light can be triggered (Güler et al., 2008).

Circadian and Acute Impacts of Light

In humans, cognitive performance remains relatively stable in well-rested individuals during the waking day. However, cognitive performance declines sharply if wakefulness is further extended into the biological night (Gaggioni et al., 2014). This non-linear change results from the interplay between the circadian system, temporally organising physiology and behaviour, and sleep homeostasis, keeping track of time awake and the building up of sleep need. Disturbances to the fine-tuned interplay between both systems, such as jetlag, shift work or partial sleep loss, result in cognitive impairment (Gaggioni et al., 2014). Light is the primary environmental cue entraining the SCN, and the circadian phase can be altered depending on its timing (Duffy et al., 1996). Light delivered in the evening and at night, up to the minimum of core body temperature (i.e., around 6 a.m., in individuals with a standard ~11 pm–7 am sleep schedule), delays the circadian phase; morning light, following the core body temperature trough, advances circadian phase. The phase-shifting impact of light has been proven with monochromatic blue (~460 nm) or polychromatic, blue-enriched light sources, but when compared with standard polychromatic bright white light sources of similar photon density, both similarly advance or delay the circadian phase (Lockley et al., 2003; Revell et al., 2012; Smith et al., 2009; Smith & Eastman, 2009). Furthermore, a longitudinal study tracking light exposure over a 7-day period found evidence that light exposure patterns were associated with specific measures of sleep health and performance (Didikoglu et al., 2023). Light can therefore have an indirect impact on alertness, sleep, and cognition through phase shifting of circadian rhythms.

Light exposure can also have acute NIF impacts on alertness, sleep, and cognition, all with a sensitivity shifted toward shorter wavelength light (~460 nm) (Cajochen et al., 2005; Chellappa et al., 2013; Lockley et al., 2006; Rahman et al., 2014; Santhi et al., 2012; Vandewalle, Maquet, et al., 2009). Though, it should be noted that the acute NIF effects of light may not be due to a direct result of melatonin suppression through melanopsin-ipRGCs (Blume et al., 2022). Light's impact on alertness has been measured with subjective and objective measures with both kinds showing that light exposure increases alertness. Light exposure reduces alpha, theta, and low-frequency activity, which are correlates of sleepiness (Cajochen et al., 2000; Lockley et al., 2006). Furthermore, light exposure also reduces the incidence of slow eye movements, which are indicators of inattention that increase in response to sustained wakefulness, especially during the biological night (Cajochen et al., 2000). Electroencephalogram (EEG) correlates of alertness are more affected by blue (460 nm) light exposure than longer-wavelength light or darkness (Chellappa et al., 2013; Lockley et al., 2006; Santhi et al., 2012). Furthermore, a study using a custom visual display unit that could vary melanopic-irradiance found that melatonin and subjective sleepiness scores were modulated after evening exposure in healthy participants (Allen et al., 2018). The impact of light on alertness has not always been consistently shown during the day (Dumont & Carrier, 1997; Lok et al., 2018; Segal et al., 2016; Smolders et al., 2018) and may depend on the experimental context (participants laying down and/or maintained in dim light or darkness before experimental light exposure and/or sleep loss) and light parameters (duration, intensity, and spectrum). A recent meta-analysis suggests that subjective and objective measures of alertness are improved by light exposure, with subjective alertness being improved by light exposure during both the day and night. Light sources with a higher correlated

colour temperature (CCT), therefore more blue-enriched light sources, appear to be more effective at modulating alertness than light sources with a lower CCT (Mu et al., 2022). A further systematic review concludes that short wavelength light and high-intensity white light exposure influence alertness, but this depends on certain factors such as time of day (Siraji et al., 2022).

In rodents, ipRGCs were reported to directly favour sleep during light exposure, but they also promote alertness during darkness, i.e., the absence of light is signalled by ipRGCs (Pilorz et al., 2016; Tsai et al., 2009). Translation of the latter finding to humans, where ipRGCs would favour sleep during darkness, is difficult to assess. However, one study in humans reported there was reduced performance in a vigilance task when participants were pre-exposed to red (635 nm) light, which could putatively be equivalent to darkness ipRGC signalling (Van Der Meijden et al., 2018). IpRGC output was also found to directly affect sleep homeostasis response to sleep loss in rodents (Tsai et al., 2009). In line with this, blue-enriched light was reported to affect sleep homeostasis in humans, most likely acting through the ipRGC pathway (Chellappa et al., 2013; Santhi et al., 2012). Furthermore, a study in rodents provided direct evidence that chemogenetic activation of ipRGCs increased alertness (Milosavljevic et al., 2016).

Beyond the modulation of alertness and sleepiness, light can also acutely improve cognitive performance (Vandewalle, Maquet, et al., 2009) typically within 30 min (being the typical time resolution of the experiments) at night (Cajochen et al., 2000; Daurat et al., 1993; Lockley et al., 2006) and during the day (Phipps-Nelson et al., 2003; Rüger et al., 2006). However, as for alertness, daytime impacts are not consistently reported (Lok et al., 2018; Segal et al., 2016; Smolders et al., 2018). The performance-enhancing effects of light on cognitive functions have been shown for visual search, digit recall, serial addition–subtraction, two-column addition, logical reasoning tasks, letter cancellation tasks, and simple reaction time tasks (Daurat et al., 1993; Phipps-Nelson et al., 2003; Rüger et al., 2006; Vandewalle, Maquet, et al., 2009). Blue (470 nm) monochromatic light exposure caused a higher amplitude level on the P300, an event-related task when compared to other monochromatic light sources (Okamoto & Nakagawa, 2015). There is a need for further research on how light exposure impacts cognitive functions; a systematic review reported that improvement in cognitive performance by light may depend on the spectral composition of the light, the time of day, and task complexity (Siraji et al., 2022).

In rodent models, light has been reported to affect memory, and this performance impact of light on memory is mediated by ipRGCs and rod/cone photoreceptors (Fernandez et al., 2018; Tam et al., 2016). Further research in rodents identified that the spatial-memory-promoting effects of light treatment are mediated by a visual circuit involving the vLGN/IGL, nucleus reuniens, and the hippocampus (X. Huang et al., 2021). A resting-state fMRI study in humans during the daytime has shown that 30 min of blue (469 nm) light exposure can increase brain connectivity within networks associated with working memory and attention (Killgore et al., 2022). Longer exposure (~8 h) to blue-enriched light during the daytime also leads to improved working memory, procedural learning, and processing speed in sleep-restricted young adults (Grant et al., 2021). Another study reported that long daytime exposure (~10 h) to high melanopic content, blue-enriched white LEDs led to an improvement in daytime cognitive function, which may not be due to changes in daytime alertness (Lok et al., 2022). However, further research in humans is needed to understand how light can affect alertness and cognition

during the day and how it impacts memory during its encoding, consolidation, and retrieval phases in humans (Hasan et al., 2021).

NIF Brain Circuits of Light, Impact on Cognition and Inter-Individual Variations

The brain pathways of ipRGC signalling are extensively investigated in animal models (Tri & Do, 2019). Melanopsin-expressing ipRGCs (mainly M1 and M2 subtypes) project via the retinal hypothalamic tract to numerous subcortical and cortical areas of the brain, including the SCN and OPN, upstream of the Edinger–Westphal nucleus, driving pupil constriction (Baver et al., 2008). IpRGCs innervate the ventro-lateral preoptic nucleus (VLPO), subparaventricular nucleus, and lateral hypothalamus, involved in sleep–wake regulation (Hattar et al., 2006; Z. Zhang et al., 2021). They also project to the amygdala and the perihabenular region (Fernandez et al., 2018) involved in emotional responses and mood. IpRGC efferences reach the upper brainstem superior colliculus, notably controlling eye movement, and are involved in attention (Lyon et al., 2010). IpRGCs also reach the thalamus in the intergeniculate leaflet and the pulvinar, a crossroads between cognition, attention, and alertness (Saalmann et al., 2012), as well as in the LGN (Tri & Do, 2019).

The SCN has multiple direct and indirect projections to key brain regions for sleep– wake regulation such as the VLPO, paraventricular nucleus of the hypothalamus, dorsomedial nucleus of the hypothalamus, locus coeruleus, and the pineal gland, which secretes melatonin (Scammell et al., 2017). Therefore, environmental light information can be conveyed directly by the widespread projections of ipRGCs to subcortical brain regions, but also indirectly through modulating the SCN and its downstream targets. These widespread projections underlie the multiple NIF and visual functions of ipRGCs. Apart from a few studies in primates, most of these projections have been identified in laboratory mouse lines. However, these are nocturnal animals; most often they are devoid of melatonin and have their own cognitive abilities (Tri & Do, 2019). Translation to humans is therefore not straightforward.

Neuroimaging the impact of light on NIF cognitive functions in humans provides insight into the brain regions involved beyond the first retinal projections. First, a positron emission tomography (PET) study and a functional magnetic resonance imaging (fMRI) experiment investigated the impact of polychromatic white light exposure on cognitive activity during an attentional task during the day and at night. These studies demonstrated an association between light exposure and enhanced responses to the attentional tasks in the thalamus pulvinar, as well as in cortical areas (Perrin et al., 2004; Vandewalle et al., 2006).

Several fMRI studies of the NIF impacts of light followed these initial investigations. Studies using blue monochromatic light sources proved that the effect of polychromatic light modulation on brain activity, as seen in the PET and fMRI studies, was mostly dependent on blue-wavelength light, as compared to other longer-wavelength light sources (Daneault et al., 2014; Vandewalle, Archer, et al., 2011; Vandewalle et al., 2010, 2018; Vandewalle, Gais, et al., 2007; Vandewalle, Schmidt, et al., 2007). Further light fMRI studies looked at working memory or emotional

processing tasks. These studies found that brain activity increased in the thalamus, hippocampus, and amygdala regions, as well as in the prefrontal, parietal, temporal, and insular regions involved in the ongoing cognitive process in response to light (Vandewalle, Maquet, et al., 2009). In other studies, aspects of cognition such as working memory and emotional anticipation were found to be modulated after the ending of a blue-wavelength (469 nm) light exposure period (up to 40 min after 30 min of light exposure) (Alkozei, Smith, & Killgore, 2016; Alkozei, Smith, Pisner, et al., 2016). This lasting effect of blue-wavelength (496nm) light was also reported to be associated with enhanced neural efficiency on the Multi-Source Interference Task, which is a complex cognitive task when compared to amber light exposure (Killgore et al., 2020).

FMRI studies that reduced blue-wavelength (473 nm) light exposure to less than a minute indicated that subcortical areas appeared to be first affected by blue-wavelength (473 nm) light while performing an executive task with increased activity in the pulvinar, thalamus, and brainstem, as well as the amygdala, in an emotional context (Vandewalle et al., 2010; Vandewalle, Schmidt, et al., 2007). Still using short light exposure (30 s), a recent study further supported that amygdala activity was affected by light. Amygdala activity appeared, however, to be suppressed during exposure to warm long-wavelength enriched light (2800 K) (McGlashan et al., 2021). This apparent discrepancy may arise from protocol and data processing differences, and in particular, the fact that participants were not engaged in any cognitive process (i.e., resting-state fMRI recordings).

Beyond its spectral quality, the impact of light on cognition appears to depend on the circadian phase and homeostatic sleep pressure. The impact of blue (473 nm) light on brain responses to a working memory task was stronger in the morning, particularly after sleep deprivation, compared to the evening a few hours before habitual sleep onset (Vandewalle, Archer, et al., 2011). Importantly, light does have an impact on alertness, sleep, and cognition in the evening, which may be dependent on its spectral content with LED blue-enriched screens having a greater impact than non-LED screens, though the study only included male participants (Cajochen et al., 2011). The modulatory effect of sleep homeostasis on the NIF impact of light on cognitive brain function is further reinforced by investigation in individuals with different variable-number (4 or 5) tandem-repeat in a portion of the PERIOD3 gene, a polymorphism associated with differences in sleep homeostasis, and vulnerability to sleep loss. Individuals homozygous for the 5-repeat genotype (PER35/5), most vulnerable to sleep loss, showed more light-induced increases in ongoing cognitive brain activity, putatively, as if the light was able to rescue part of the sleep-loss-induced changes (Vandewalle, Archer, et al., 2009).

Aside from sleep homeostasis and the circadian phase, ageing and sex may contribute to variability in the NIF impact of light. A study assessed the association between ageing and light sensitivity. Ageing was found to reduce the NIF impacts of blue-enriched light on melatonin secretion, slow-wave activity, subjective sleepiness, and sustained attention when comparing blue-enriched and non-blue-enriched polychromatic lights in young and old populations (Chellappa et al., 2021). Healthy older individuals showed a reduced impact of blue (480 nm) monochromatic light on executive brain response compared to younger individuals, and this difference was not fully accounted for by the difference in age-related lens opacification (Daneault et al., 2014).

The latter opacification can ultimately lead to the development of cataracts, which is another aspect of ageing that may affect light's impact on the NIF system. There are contradictory findings about the benefit of implanting blue-filtering lenses for cataract surgery. Compared to older individuals with natural lenses, individuals implanted with novel lenses because of cataracts were found to show a larger impact of light on cognition and sleep (Chellappa et al., 2019). In line with this, a resting-state fMRI study showed that alteration in blue light transmittance, through the implantation of blue-filtering lenses, can improve NIF responses such as alertness (Sobczak et al., 2021). In contrast, the impact of light on fMRI brain responses to a working memory task was found to be similar in individuals with natural lenses or with novel lenses following cataract surgery (Daneault et al., 2018). Discrepancies between studies may arise from the delay between the experiment and the surgery, which was longer in the latter study, potentially suggesting that there was a slow adaptation of the NIF impact of light over the time period.

Recent research has highlighted the importance of individual differences in light sensitivity, with individual traits including age, sex, chronotype, genetics, and ethnicity likely influencing individuals' sensitivity to light. Given that individuals in industrial societies spend an increasing amount of time indoors under artificial light, it is important to understand inter-individual differences for the development of lighting recommendations and effective individually targeted integrative lighting products (Chellappa, 2021). To close the knowledge gap of inter-individual differences, researchers have proposed key steps for the future and key research questions that need to be addressed (Spitschan & Santhi, 2022). Furthermore, indoor lighting recommendations to support NIF functions during the daytime, evening and nighttime have been developed based on scientific consensus, which is measured in mel EDI lux (Brown et al., 2022).

Collectively, the findings demonstrate that light and particularly its blue wavelength content can impact NIF brain functions (**Figure 1-3**-A), and inter-individual differences play a role in light sensitivity. The mechanism of light's impact most likely first involves the activation of subcortical brain regions that can then affect cortical activity based on the ongoing cognitive process. A detectable performance change could occur if the light's impact is strong and/or long enough. This scenario should be verified and refined through higher-resolution neuroimaging. The recent advent of ultra-high field (UHF) MRI at 7 Tesla opens access to new spatial scales with functional studies at ~1 mm directly linked to direct structural observations at the sub-millimetre scale (0.02–1 mm) and inferences about microscopic properties (<0.02 mm; e.g., myelin content and neurite density) (L. J. Edwards et al., 2018; H. Zhang et al., 2012). UHF-MRI will help resolve, for instance, the particular case of the impact of light on the hypothalamus in humans and especially on the SCN. An initial PET study suggested a reduction in the impact of light on the hypothalamus, over a region encompassing the SCN, after exposure to light (Perrin et al., 2004). A recent 7T fMRI study further reported reduced activity in an anterior part of the hypothalamus encompassing the SCN during exposure to different monochromatic light conditions (Schoonderwoerd et al., 2022). While research in nocturnal rodents reported a decrease in SCN activity following light exposure, in line with the PET study, this study suggests that SCN activity is increased during light exposure, in contrast to the 7T MRI study (Sharifpour et al., 2022). Future research will therefore have to segregate the response of the numerous light-sensitive nuclei of the hypothalamus in humans.

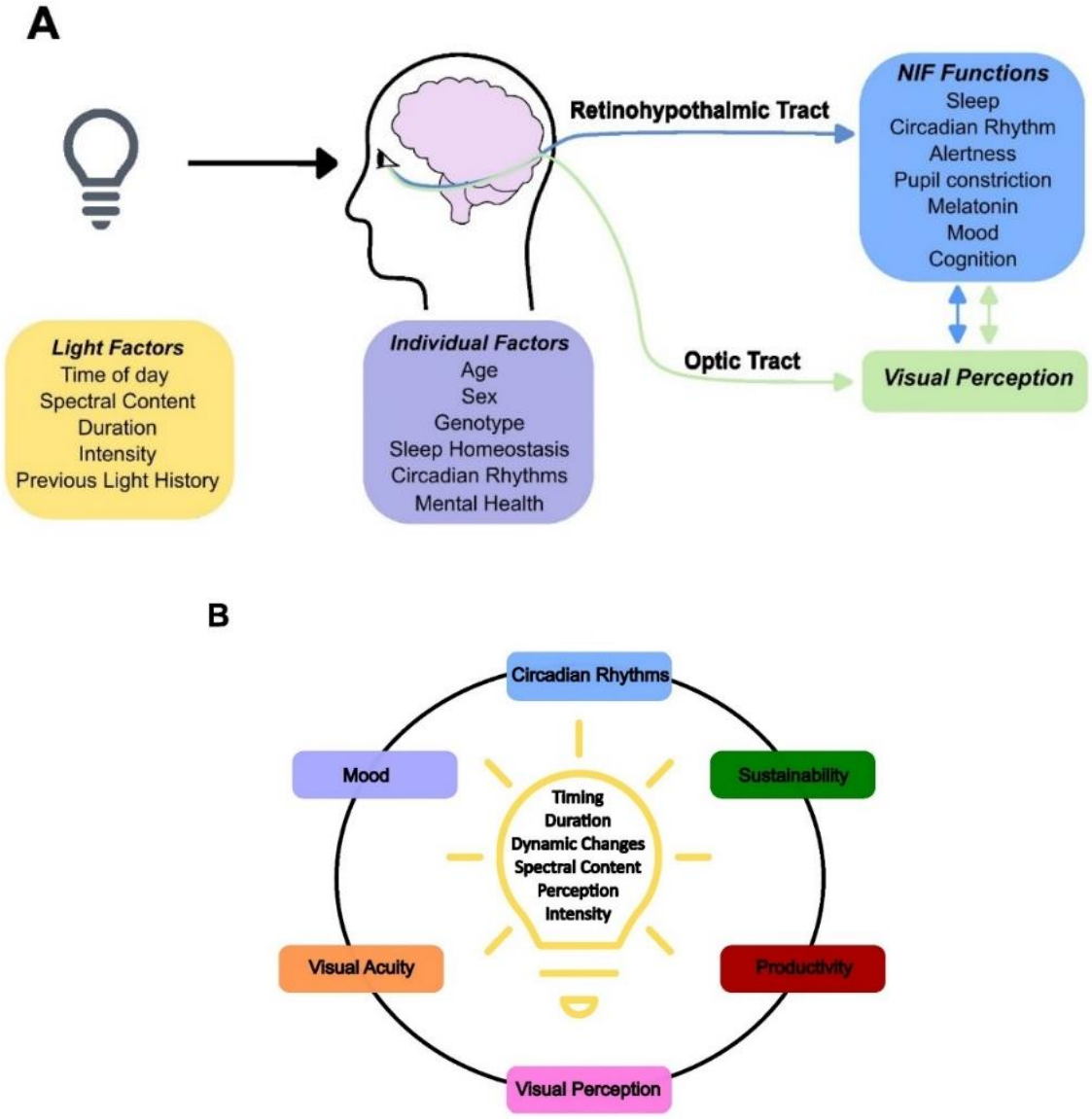


Figure 1-3. Light's impact image forming (IF) and non-image forming (NIF) pathways. (A) Light signal reaches the central nervous system via the retinohypothalamic and optic tracts of the optic nerve to affect IF and NIF functions. Light impact on NIF functions depends on light factors and individual factors. **(B)** The industrial concept of integrative lighting aims to design individually tailored dynamic lighting accounting for visual perception and acuity, together with light's impact on NIF functions, including mood, circadian rhythms, productivity (i.e., attention/alertness), and environmental sustainability. NIF's consideration of integrative lighting largely lacks a strong scientific basis.

Light's Influence on Human Cognition Is Mediated through Melanopsin Photoreception

Activation of ipRGCs using chemogenetics in mice revealed many of the direct functional targets of ipRGCs (Milosavljevic et al., 2016). However, isolating each retinal photoreceptor's influence on NIF functions in humans is more difficult than in animal models, as genetic and molecular techniques are not available. Therefore, the evidence for the role of melanopsin-expressing ipRGCs in NIF responses, including cognitive brain activity, has been inferred indirectly. Aside from colour-blind individuals (Ruberg et al., 1996), rare completely blind individuals with no functional rods and cones but who still display intact NIF responses have constituted a unique human model to isolate ipRGCs' intrinsic photoreception (Czeisler et al., 1995). Despite their complete lack of vision, these individuals have some awareness of light and can correctly guess the presence of blue (480 nm) monochromatic light exposure when presented in a two-alternative forced-choice task (Vandewalle et al., 2013; Zaidi et al., 2007), potentially because of a reduction in EEG alpha power over the occipital cortex (Vandewalle et al., 2018). Subjective sleepiness and EEG correlates of alertness also appear to be improved with blue (480 nm) monochromatic light exposure (Zaidi et al., 2007). Functional imaging of these individuals found that exposure to blue (480 nm) monochromatic light increases pulvinar and cortical activity related to ongoing executive activity (Vandewalle et al., 2013). More recently, an fMRI study compared healthy controls to a group of patients suffering from Leber's Hereditary Optic Neuropathy, a disease characterized by RGC degeneration but with a relative sparing of ipRGCs. When compared to the healthy control participants, blue (480 nm) relative to red (620 nm) monochromatic light exposure increases activity over the occipital cortex in patients. Similarly, brain responses to an executive working memory task were larger in patients over the frontal cortex compared to control participants (Evangelisti et al., 2021).

Further neuroimaging studies in healthy volunteers (i.e., no potential bias can arise from pathology) aimed at isolating melanopsin-ipRGCs' impact on NIF brain functions. An initial study based its protocol on melanopsin bistable properties and aimed to show that prior light exposure to longer-wavelength light would increase the impact of the subsequent light exposure, as it would presumably regenerate melanopsin to its phototransducible form. The findings were in line with this assumption as pre-exposure to orange light (~590 nm) increased the subsequent impact of a test light on prefrontal and pulvinar executive response (Chellappa et al., 2014). This implied that prior light history, or photic memory, can influence the NIF impact of light on cognitive brain activity. Other fMRI studies used metameric light stimuli to isolate ipRGC-driven brain activations. Metameric light sources vary light wavelength composition to stimulate a single photoreceptor type while maintaining the visual properties of the light source (Tow et al., 2017; Viénot et al., 2012). Melanopsin-geared metameric light stimulation led to increased cortical activity in the frontal eye field region, part of the ventral visual field during a simple dot-fixation task (Tow et al., 2017). In addition, and still using metameric light exposure, melanopsin-geared light flickers < 0.5 Hz in four participants led to significant fMRI signal change over the occipital cortex (Spitschan et al., 2017), while flicker ≥ 0.5 Hz in three participants failed to do so (Spitschan et al., 2016). This is presumably in line with the sluggish response time of ipRGCs. Further studies, using metameric light sources with other more cognitively demanding tasks,

may elucidate wider brain activations directly dependent on melanopsin photoreception. Although many studies have reported increased brain activity in regions involved in cognitive control, whether this increase extends to the behavioural level is still under debate (Lee et al., 2021).

A few recent studies investigated the impact of continuously variating or dynamic light on NIF responses. This is referred to as “dynamic lighting” consisting of varying the spectral content and intensity of the lighting over the course of 24h to mimic the natural light-dark cycle. They report that dynamic light as compared to static light may be more efficient in triggering NIF responses, as indexed through melatonin suppression and objective sleep measures (Geerdinck et al., 2016; Stefani et al., 2021). Another study found dynamic indoor lighting at the workplace during the daytime advances melatonin onset and peripheral heat loss in the evening, which can be beneficial for people with delayed circadian rhythms (Benedetti et al., 2022). Further, dynamic lighting can be also beneficial for circadian adaptation to shifted sleep–wake schedules (Rahman et al., 2022). The respective roles of spectral and illuminance changes cannot be discriminated yet, in terms of the beneficial effects of dynamic light. However, it is interesting to note that their interplay seems to be quite well-captured in the measure of melanopic equivalent daylight illuminance (Brown, 2020; Vetter et al., 2021), further reinforcing the idea of a prominent role of ipRGCs for NIF functions and warranting further research on dynamic light’s impact on cognitive brain function, alertness, and sleep.

Emotional Processing and Mood

It is established that light can affect mood, and how our modern light environment impacts our mood needs to be carefully considered. LEDs have been beneficial in clinical settings for bright light therapy, which is used to treat seasonal and non-seasonal depressive disorders, demonstrating that light can modulate mood over long periods of time (Even et al., 2008; Terman & Terman, 2005). Seasonal affective disorder (SAD) depressive episodes are believed to be triggered by the seasonal shortening of daylight hours, as supported by its higher prevalence at higher latitudes (Magnusson & Partonen, 2005). SAD patients were also reported to show a different impact of blue and green monochromatic light in the hypothalamus in an emotional task during winter (Vandewalle, Hébert, et al., 2011). Altered light modulation of emotional processing may therefore play a role in SAD aetiology, together with retinal dysfunction and inappropriate circadian entrainment (Lavoie et al., 2009; Lewy et al., 2006). Healthy human beings show seasonal changes in cognitive brain responses (Meyer et al., 2016), which may contribute to the cognitive impairments reported in individuals suffering from SAD (Magnusson & Partonen, 2005) and to the known seasonality in the symptoms of several other psychiatric disorders (Barbini et al., 1995).

Aberrant light in the evening may be particularly detrimental to mood, as shown in rodent models (Legates et al., 2012). Light can delay the circadian timing system when administered in the evening, so evening light could contribute to suboptimal circadian entrainment, as found in SAD (Lavoie et al., 2009; Lewy et al., 2006). As most human beings have a circadian period slightly longer than 24h (Czeisler et al., 1999), morning light is needed to advance the clock and favour earlier sleep times, and so morning light is typically considered beneficial. Whether more light in the morning can rebalance excessive evening light exposure to improve mood, sleep, and wellbeing is currently under investigation (Kawasaki et al., 2021).

IpRGC photoreception is highly likely to contribute to the therapeutic effect of light exposure. Firstly, the spectral composition of light changes over the seasons, with more blue light in the summer compared to the winter (Thorne et al., 2009). Secondly, despite contradictory results about the efficacy of blue-light therapy in the treatment of seasonal and non-seasonal major depressive disorders, some studies reported that blue-light therapy, including using LEDs, is an effective treatment for SAD, but importantly requires lower irradiance and/or shorter exposure duration than standard white-light therapy (Do et al., 2022; Glickman et al., 2006; Strong et al., 2009; Terman & Terman, 2005), which may favour treatment compliance. Thirdly, certain individuals with genetic mutations within the melanopsin gene have an increased risk of SAD (Roecklein et al., 2013). Finally, mice lacking melanopsin do not show depressive behavioural traits seen in wild-type animals exposed to aberrant light in the evening (Legates et al., 2012). In addition, selective activation of ipRGCs though the use of chemogenetics in mice models found a behavioural shift to an increased state of alertness and/or anxiety (Milosavljevic et al., 2016).

Furthermore, retina-brain pathways, which mainly involve melanopsin-ipRGCs, have been reported to be involved in light impacts on mood: the SCN-dependent pathway and the SCN-independent pathways (Maruani & Geoffroy, 2022). Recently, M4-ipRGC subtypes have been implicated in a multi-synaptic pathway reaching the habenula and involved in mood regulation

independently of the SCN and therefore circadian entrainment. At least in mouse models, this may be one of the pathways that are involved in the antidepressant effects of light (L. Huang et al., 2019). Whether a similar functional pathway exists in humans is not known, but a neuroimaging study has found a modulation of the habenula in response to changes in luminance with a time-of-day effect (Kaiser et al., 2019). The studies discussed above provide evidence for the involvement of melanopsin-ipRGCs in emotion and mood regulation. A theoretical model has been proposed for the integration of Beck's cognitive model with light-sensitive neural circuits that are part of the emotional processing systems in the brain. Beck's cognitive model for depression suggests that the onset of depression is linked with negative biased cognition, through the process of consistent biased attention, biased processing, and biased rumination. Key ipRGC brain circuits include the involvement of ipRGC-hypothalamic regions and the pituitary and pineal glands, ipRGC-limbic regions, and ipRGC-thalamic regions that may underline the antidepressant effects of light. The proposed model will help with more targeted brain research on the anti-depressive effects of light (Chen et al., 2021).

Functional imaging studies have revealed the critical roles of ventromedial and dorsolateral PFC, which have opposite activities, in depression (Koenigs & Grafman, 2009). PET studies showed that glucose metabolism in the ventromedial part of the prefrontal cortex (vmPFC), including the subgenual anterior cingulate cortex and orbitofrontal gyrus, is higher in depressed patients compared to healthy subjects (Drevets et al., 2002; Mayberg et al., 1999). A similar result was reported for brain activity in the vmPFC using resting state fMRI. Antidepressants can therefore help patients recover by affecting the PFC activity, and it has been shown that antidepressants are associated with decreased activity in vmPFC (Greicius et al., 2007). Recently, an fMRI study has reported reduced PFC activity (including the subgenual anterior cingulate cortex and orbitofrontal gyrus) in response to light as a function of luminance level. The suppressed brain activity is similar to the impact of chemical antidepressants, which could indicate the anti-depressive role of light in the PFC subregions (Sabbah et al., 2022).

Beyond the potential role of light in mood disorders, the effect of indoor lighting on emotional perception has been investigated in a healthy population. A study focused on investigating whether specific characteristics (illuminance and CCT) of a light source can influence emotional perception; there was no significant effect of light characteristics on negativity bias during an emotional oddball task. However, lower CCT (2700 K) (but not illuminance) was associated with a decrease in an individual's negative response bias during a face-judgement task. The results suggest that the specific characteristics of a light source may be important for instant emotional perception in a healthy population, with illuminance and CCT having different roles. This light moderation of negative bias was task-dependent though (Y. Li et al., 2021). While this study highlights the potential impact of indoor light on emotion, overall, the research on light's (daylight and electrical) effect on light impressions and subjective mood states remains inconclusive (Kong et al., 2022).

Adverse Impacts on Sleep and the Particular Case of Teenagers

A quick calculation using the freely available Luox online tool (Spitschan, Mead, et al., 2021) shows that, based on the same photopic lux, a white LED gives about 27% more melanopic irradiance than a fluorescent light source and about 40% more than an incandescent bulb. Since current research indicates that NIF responses occur over a log scale (e.g., (Brainard et al., 2001; Cajochen et al., 2000)), this may result in a relatively limited increase in the biological impact of light. The timing of the widespread use of LED devices may therefore be more problematic than the increased blue content. Artificial lighting may be very problematic in the evening, particularly given the widespread use of screen devices that have allowed for activities that were previously difficult in darkness or under dim light.

Light exposure in the evening and at night significantly delays melatonin secretion and circadian phase, increases alertness (Cajochen et al., 2005), and disturbs subsequent slow-wave sleep and sleep homeostasis processes (Chellappa et al., 2013). For individuals with late chronotypes, which are characterized by a longer circadian phase and/or shallower increase in sleep need (Mongrain et al., 2006), this is very likely to delay sleep time. Late chronotypes may also be more sensitive to light (Rufiange et al., 2002), further exacerbating the NIF impacts of evening light. Recent research shows that it is plausible that the advent of electric lighting contributed to the spreading of sleep timing across individuals in modern society, putatively by delaying sleep times, particularly in late chronotypes (Wright et al., 2013).

Teenagers may be at particular risk of the adverse impact of evening light. They naturally tend to be later chronotypes (Ricketts et al., 2022) and still need a lot of sleep. However, they are required to wake up early due to school times. They are also high consumers of evening light through electronic device screens. There is some evidence in teenagers that evening light delays melatonin secretion, circadian phase, and sleep, as in adults (Gasperetti et al., 2020; Van Der Lely et al., 2015). In another study, no significant changes in sleep measures were reported, however, when teenagers were exposed to a short period (1 h) of screen use before habitual bedtime (Heath et al., 2014). Studies focusing on teenagers remain scarce, making it difficult to draw concrete conclusions about the NIF effects of light in this age group. Manipulating light exposure, particularly the timing of light exposure, is nevertheless being recommended as a potential intervention aimed at improving sleep in teenagers (Gasperetti et al., 2020). Importantly, it seems that imposing early restriction times on the use of screen devices in teenagers while not requesting any changes in ambient light arising from other light sources, favours earlier sleep times (Perrault et al., 2019). This finding may be associated with reduced exposure to blue-enriched LED screen light and may also have to do with the (social media) activity associated with LED screen exposure. In other words, light per se may not be the only factor curtailing sleep, but also what light allows one to do in the evening. The impact of light exposure on teenagers is a unique situation, and we have only briefly touched upon the subject here. Physiological and environmental factors most likely contribute to the sleep–wake changes seen in developing adolescents. How light environments (e.g., devices used in the evening, school and home lighting, etc.) exacerbate the changes seen in the sleep–wake cycle during adolescence is still being researched (see review (Ricketts et al., 2022)).

The term “blue light hazard” (BLH) is used to describe the ophthalmic phenomenon where there is potential photochemical damage caused to the retinal tissues of the eye by short wavelength light (Ouyang et al., 2020; Van Norren & Vos, 2015). The potential damage from the BLH region is particularly prominent for prolonged and/or intense exposure to wavelengths < ~440 nm, especially when arising from relatively focal light sources. The BLHL region is therefore distinct from the NIF impacts of diffused light, which have a peak around 460–480 nm wavelength. While there is evidence that prolonged reduction of blue wavelength content of a light source (e.g., through blue-light blocking filters) reduces photochemical damage to the retina in rodents (X. Liu et al., 2019; Vicente-Tejedor et al., 2018), there is no evidence to support that exposure to blue light from LEDs increases the risk of photochemical injury for humans under normal exposure conditions. The relationship between LEDs and long-term adverse effects is still not conclusive; there is evidence of an association between age-related macular degeneration and sunlight, but whether this extends to artificial light sources is unknown (Zhou et al., 2018; Ziegelberger et al., 2020). Studies assessing LED screen devices and low-energy light bulbs have found no evidence of the blue-light hazard exposure limits (Bullough et al., 2017; O’Hagan et al., 2016).

The position of the Commission Internationale de l’Eclairage is that there is no risk of damage to the retina from the BLH hazard region from LEDs or white-light sources in general during normal use. However, there should be increased caution when exposed to optical radiation that approaches the BLH exposure limit that occurs for many days and with a continuous period of exposure (*CIE Position Statement on the Blue Light Hazard*, 2019). A special concern may also be required with certain groups; for instance, it is recommended that blue light is not used for children’s devices, as it may be too bright (CIE Position Statement on the Blue Light Hazard, 2019)(CIE Position Statement on the Blue Light Hazard, 2019), and there is evidence that blue light transmission through the lens changes with advanced age (Daneault et al., 2014, 2018). One should also avoid staring at the sun for more than 0.5 s, as this can cause solar retinitis: a type of damage that is naturally avoided by the eviction reflex of closing the eye against bright light (Behar-Cohen et al., 2011). Apart from BLH, solar retinitis, and the potential negative impact on mood reviewed in a previous section, exposure to light has been linked to other negative outcomes. IpRGC photoreception has been associated with photophobia in migraines, and therefore blue light should be used with caution in individuals suffering from migraine episodes (McAdams et al., 2020). The association between artificial light at night and cancer risk has also been studied, but the results from studies are inconclusive due to limitations with accurately assessing light exposure (Jones, 2021). However, two case-control studies assessed exposure to light using satellite images and were able to differentiate light wavelengths. The studies found outdoor light in the blue spectrum was positively associated with an increased risk of breast, prostate, and colorectal cancers (Garcia-Saenz et al., 2018, 2020). Artificial light is a modifiable cancer risk factor and therefore a better understanding of the association between artificial light at night and cancer is needed, and it is important for developing recommendations for the use of artificial light at night (Jones, 2021). Furthermore, digital eye strain refers to eye problems

caused by the prolonged use of digital devices, including eye strain, dry eyes, blurred vision, headaches, and neck pain.

Currently, the evidence to support the use of blue-blocking lenses and filters for digital eye strain is inconclusive and more randomized controlled trials are needed (Lawrenson et al., 2017; Sheppard & Wolffsohn, 2018; Singh et al., 2021). Finally, visual acuity also appears to be affected by focusing on screen devices at a close distance and for a prolonged time, raising concerns about a predicted increase in myopia, though there are many other risk factors involved in myopia development (Xiang & Zou, 2020). While time spent outdoors has been seen to have a protective effect on myopia onset (Xiong et al., 2017). There is evidence from mice studies that ipRGCs have a role in myopia progression and ocular growth (A. L. Liu et al., 2022). However, the exact impact of screen-emitted light on visual acuity still needs to be thoroughly assessed (Xiang & Zou, 2020). Furthermore, it has been proposed that prolonged exposure to LEDs may prompt myopia development through disruption of retinal circadian rhythms. Research in animal models supports a negative link between LEDs and the disruption of retinal circadian rhythms and mammalian refraction development. More research is needed in humans, as currently there is only circumstantial evidence of this link (C. Zhang et al., 2023). Overall, there is concern about the potentially harmful effects of blue light that is increasingly available in white LEDs, e.g., through LED screen devices, but also for medical purposes (Ouyang et al., 2020; Wong & Bahmani, 2022). However, the increase in blue light in LEDs is unlikely to be the main driver of health issues; other key factors need to be taken into account when discussing health issues surrounding lighting, including sleep–wake schedules, circadian rhythms, duration of screen use, evening and late-night use of light sources and screen devices, and repeated long-term exposure. Here, we have briefly highlighted some of the impacts of light on human health, but light may potentially have a much broader influence on human health (see review (Boyce, 2022)). Understanding the role of light in health and wellbeing needs to be placed in context, as many other factors need to be considered when discussing light's influence on human health (Boyce, 2022). Whilst there is clear evidence that light does impact health and wellbeing, research still needs to establish how to optimize the prevention of the negative impacts of inappropriate light while maintaining visual functions and favouring positive NIF effects.

Lighting Environments

Studies are increasingly looking at how altering light environments in the "real world" may improve health and wellbeing. Optimizing lighting with blue-enriched light sources in offices had a beneficial impact on subjective alertness, mood, performance, and sleep in comparison to standard lighting (Viola et al., 2008). Classrooms with blue-enriched light sources were associated with a beneficial impact on cognitive performance in students (Keis et al., 2014). Likewise, blue-enriched light treatment can improve sleep quality and cognitive function in Alzheimer's patients (Cremascoli et al., 2022; Kim et al., 2021). In patients with disorders of consciousness (DOC) that still show detectable signs of a sleep–wake cycle (this is not the case in many DOC patients), blue-light treatment in the morning in combination with caffeine and melatonin treatment caused an improvement in sleep and circadian rhythms (Yelden et al., 2022). A further study looked at long-term (3.5 years) exposure to daily polychromatic light (~1000 lux) in combination with or without melatonin in multiple care facilities. In the bright light condition without melatonin, there were reduced cognitive deficits, improvements in depressive symptoms, reductions in increasing functional limitations, and improvements in sleep duration over time in the elderly. Furthermore, in combination with melatonin, bright light exposure improved aspects of sleep that improved over time with the treatment. Further long-term studies on light and/or melatonin will help to determine effects that develop slowly and have previously been missed in short-term studies (Riemersma-van der Lek et al., 2008).

Given that LEDs can be tuned almost infinitely, LED lighting has the potential to play a major role in promoting health and cognition. The concept of integrative lighting (traditionally referred to as "human-centric lighting") developed out of these new possibilities. Integrative lighting aims to take into account all the visual and NIF impacts of light to dynamically change light spectral content and intensity over the day, with a potential benefit for cognitive performance, sleep regulation, emotion, mood, and wellbeing (**Figure 1-3**-B) (Houser et al., 2020; Pimputkar et al., 2009). Considering the NIF effects, recommendations were recently proposed for indoor lighting during the daytime, evening, and nighttime (Brown et al., 2022).

Research on dynamic lighting is becoming more common; however, the number of studies is still relatively low. Currently, studies have produced mixed results with the main reported benefit of dynamic lighting being sleep-related effects due to increased light levels during the day. This may in part be due to different theoretical aims of studies, protocol differences, and different lighting scenarios (Kompier et al., 2020). Certain studies have also highlighted the sleep-related benefits of dynamically changing light spectra for hospitalized patients (Canazei et al., 2022; Geerdinck et al., 2016). A recent study looked at the impact of dynamic lighting over a longer time scale (48 h) on subjective wellness measures, cognitive performance, and sleep measures. Dynamic lighting compared to static lighting was found to be beneficial for sleep-related effects and there was also a beneficial impact on the other metrics, but this was dependent on a time of day and experimental day effect. The study provides evidence that dynamic lighting is beneficial to a "stimulated" office environment; however, no conclusive pattern emerged from the study. These considerations highlight the need for more research on dynamic lighting in larger data sets and the need to investigate how inter-individual differences impact responses to dynamic lighting (Ru et al., 2023). The optimization of dynamic light is challenging because the design of

dynamic lighting scenarios may be different depending on the aims (e.g., which NIF functions are being targeted) and the real-life environmental context. Depending on these factors, different dynamic lighting scenarios could be developed, but further research on dynamic lighting with larger datasets on longer time scales and outside of laboratory studies is still needed before successful implementation (Kompier et al., 2020). A study in a small number of healthy male volunteers showed that NIF responses to light, including melatonin suppression, sleep measures, and modulation of alertness and cognitive performance, can be caused by using white LED backlight screen devices in the evening, most likely due to the high short-wavelength content of white LEDs (Cajochen et al., 2011), as expected based on previous research using other light sources. However, the impact of year-long exposure to light in the evening and at night, including blue-enriched light is not known in humans. The knowledge gap is not new but may be even more evident now that LEDs allow for “any light, anywhere and anytime”. The success of individually targeted lighting devices will depend in part on a better understanding of the complex light-sensitive pathways of the brain and the bases of inter-individual differences in light influence on NIF physiology, including age, sex, mental health, and genotype (Chellappa, 2021). Although field interventional studies are increasingly carried out, the translation of in-lab findings to help design field studies and interventions also remains insufficient (Münch et al., 2020; Wirz-Justice et al., 2020).

Finally, as we continue to develop lighting environments that ”mimic” natural daylight, more evidence is required to understand the assumed benefits of natural daylight over electrical lighting (Wirz-Justice et al., 2020). A full discussion on natural daylight is beyond the scope of this review; however, it is important to recognize the importance of natural daylight for human health and wellbeing. Researchers have already established key knowledge gaps within the natural daylight field and have proposed research aims for the future (Knoop et al., 2020; Münch et al., 2020). How we continue to develop our electrical light environments in combination with our natural daylight environments is a complicated research question, where interdisciplinary research is no doubt needed to ensure the development of light environments that benefit human health and wellbeing.

Conclusion

We have moved away from traditional indoor lighting, which used to be of lower intensity and blue-depleted compared to natural light. White LED lighting has led to more blue-wavelength light exposure potentially closer to natural light. As individuals in industrial societies spend a large part of each day indoors under electric lighting, it is an important research question to address to better understand the NIF impacts of light. We suggest that future research on the NIF impacts of light should focus on the following research aspects. Firstly, the exact dose of light required to impact NIF physiology is not known and how the characteristics of the light source (intensity, wavelength, duration, timing, and dynamic changes) and inter-individual differences (age, sex, and genotype) will impact the NIF functions remains to be fully elucidated. Secondly, the use of high-resolution neuroimaging in humans should refine the in vivo brain wiring of the NIF impacts of light under different cognitive tasks. Thirdly, the impact of repeated and/or long-term light exposure remains to be fully characterised. Fourthly, separating the different negative impacts of light exposure, the detrimental NIF effects on mood and sleep, and the potential reduction of visual acuity is required to optimize lighting recommendations. Finally, lab findings should be more thoroughly translated to field studies, including assessing interindividual differences, e.g., between age groups (infants, young children, teenagers, and the elderly), and the visual roles of light, to make integrative lighting a concept truly based on scientific findings.

Objectives

Overall, it can be stated that research into the NIF system, since it was first predicted to exist in 1927 (Keeler, 1927) has led to a deeper understanding of the mechanism mediating the biological impacts of light on human physiology and psychological processes. However, a great deal remains to be explored, particularly in humans. In the present PhD thesis, we cannot contemplate all the proposed perspectives put forward in the conclusion of the introduction. Working in a neuroimaging lab we chose to focus mainly on the second perspective to gain a better understanding of the brain wiring underlying the NIF impacts of light. The fundamental goal was to investigate the non-image-forming impact of blue-enriched light on subcortical and cortical structures while engaged in different cognitive processes, using eye-tracking and high-resolution 7 Tesla functional magnetic resonance imaging (fMRI).

To accomplish this, we conducted a large single multimodal study (termed the HILIGHT study) consisting of neuroimaging young healthy participants, who completed three cognitive tasks whilst exposed to different illuminances (**Figure 1-4**). Participants were first screened for the exclusion criteria and then completed a structural MRI session which served as habituation to the experimental conditions. For 7 days before coming to the lab for the fMRI acquisition, participants maintained a loose sleep-wake schedule (±1 h from habitual bedtime/wake-up time). The participants arrived at the lab in the morning and were exposed to 5 minutes of bright light (1000 lux) and then maintained in dim light (<10 lux) for 45 minutes to standardise the short-term light history before completing the fMRI scan. The fMRI session consisted of three auditory cognitive tasks (executive, attentional and emotional), that probed different cognitive domains, while alternatively maintained in darkness or to short light exposure periods (30s-50s). An eye-tracking system recorded pupil measurements during all three cognitive tasks.

The data acquisition of the HLIGHT study is not finished at the time of writing this thesis, the study will be continued by my colleagues in the HILIGHT team. Likewise, each experimental chapter includes a different number of datasets, reflecting the data collection status at the time of initiating the analyses. Given the large amount of data collected and the involvement of multiple PhD students, we each investigated different aspects of the HILIGHT project. The rationale for choosing these specific brain regions we focused on in the thesis, is discussed below, based on the current NIF system literature and from a personal working perspective.

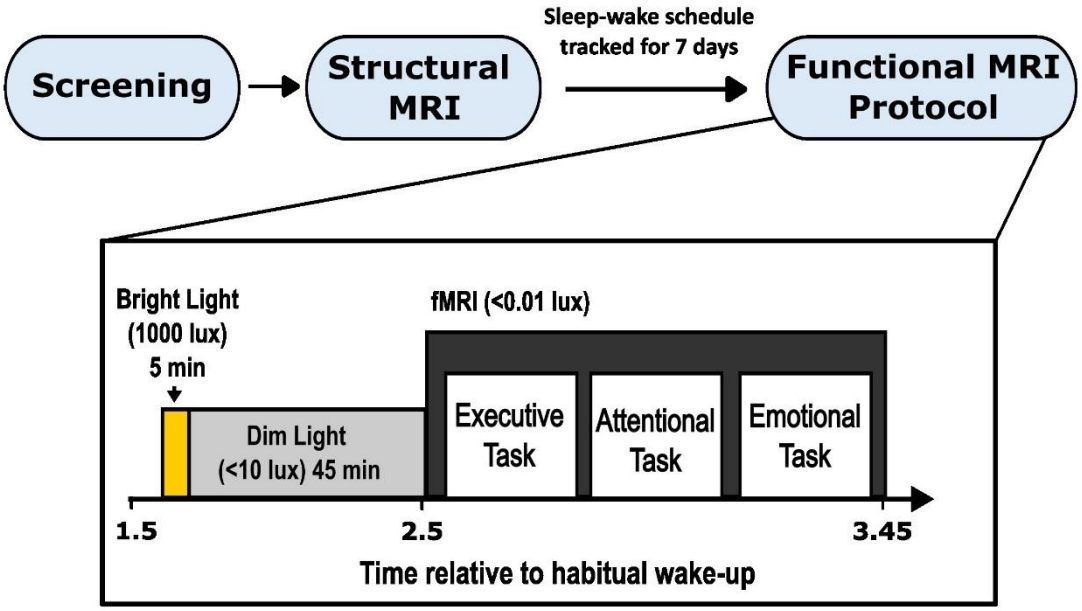


Figure 1-4 Brief Overview of the HILIGHT Protocol Design. Participants were screened for the exclusion criteria. Then came to the lab for a structural MRI session. Participants followed a loose sleep-wake schedule for 7 days before the functional MRI protocol. Time relative to scheduled wake-up (h). Following standardisation of immediate prior light exposure, participants performed an executive, attentional and emotional task in functional magnetic resonance imaging (fMRI).

The experimental part that follows consists of three chapters that are centred around three critical research objectives.

In chapter two, we investigated whether illuminance influences the processing of sensory stimulation from the viewpoint of the pupil. Before focusing on brain BOLD MRI signals in later chapters, we first reasoned that pupil measures could provide a relatively accessible first assessment of the impact of light on brain function. We considered the transient pupil dilations associated with auditory stimulation processing because they are likely driven in part by the activity of the locus coeruleus (LC).

The LC is a subcortical brain region, that is central to cognition and alertness (Aston-Jones & Cohen, 2005). Light's influence on cognition and alertness in humans is thought to be in part mediated by LC phasic activity, as evidence from a neuroimaging study suggested that the activity of the LC was modulated by light (Vandewalle, Schmidt, et al., 2007). Whilst the LC is not directly innervated by ipRGCs, it does receive innervation from the suprachiasmatic nucleus (SCN), which is densely innervated by ipRGCs (Aston-Jones et al., 2001; Tri & Do, 2019).

Pupil size is known to adapt to changes in the light environment, but transient pupil responses can also be evoked by external task events. These task-evoked pupil responses (TEPRs) are considered a non-invasive way to determine the phasic activity of the LC (Aston-Jones & Cohen, 2005; Larsen & Waters, 2018). In vivo imaging of the LC is difficult, due to its small size and location in the brain stem, however, measuring pupil size variation through eye tracking is an accessible means to assess LC activity (Keren et al., 2009). Therefore, we aimed to investigate

the TEPR associated with auditory inputs under different light levels during two of the cognitive tasks included in the HILIGHT study (the third task was not appropriate to isolate TEPRs). We hypothesized that the TEPRs would be greater under higher irradiance levels due to the stimulating NIF impact of light. We found that the TEPRs to auditory stimuli were larger under higher illuminance, and this was detected for the two cognitive tasks. We further find task-specific differences in the impact illuminance has on the different types of stimuli of each task.

At this point, it was not realistic to look at the neuroimaging of the LC to confirm its involvement in the chapter two study. For two main reasons, we only had a small number of participants with good eye tracking and fMRI data and the LC masks needed to extract activity estimates from this region were not ready. My colleague will investigate this in the future. Therefore, in chapter three we choose to look at the neuroimaging data without considering the complimentary eye tracking data.

We considered the fMRI data acquired during the study and truly investigated the subcortical circuitry underlying the stimulating impact of light. The subcortical regions of the brain have been hypothesised to be the initial sight receiving light's signal before going on to impact cortical regions based on the ongoing cognitive process (Gaggioni et al., 2014). In this study, we assessed the impact of variations in illuminance on the regional activity of the hypothalamus during two cognitive tasks.

Previous research in humans has found that the hypothalamus is influenced by light, but there are conflicting results. An initial PET study reported that light decreased the activity of an area encompassing the hypothalamus during the period of darkness immediately following the exposure (Perrin et al., 2004). Likewise, a recently published 7T fMRI study reported reduced activity of the area encompassing the SCN during light exposure (Schoonderwoerd et al., 2022). In contrast, 3T MRI studies reported that light could increase the activity of the hypothalamus and modify its crosstalk with other brain regions (Vandewalle et al., 2010; Vandewalle, Hébert, et al., 2011). The contrasting results may be due to the fact there are several light-sensitive nuclei of the hypothalamus and separating these areas by neuroimaging remains a challenge (Billot et al., 2020; Sharifpour et al., 2022). IpRGCs innervated several nuclei found in the anterior part of the hypothalamus with the SCN, the site of the master circadian clock, receiving the densest projections (Scammell et al., 2017; Tri & Do, 2019). The posterior part of the hypothalamus also receives ipRGCs projections into the lateral hypothalamus (Tri & Do, 2019).

We investigated whether the human hypothalamus nuclei could contribute to the stimulating impact of light on cognition and whether there are regional differences in hypothalamus activity to illuminance variation. We hypothesised that higher illuminance would have a stimulating impact on the activity of the anterior hypothalamus due to its dense innervation by ipRGCs. In contrast, we found that higher illuminance triggered an activity increase in the posterior part of the hypothalamus that encompasses the lateral hypothalamus and evoked a decrease in activity over the anterior and ventral parts of the hypothalamus. Overall, there is a distinct local dynamic of different hypothalamus regions that underlie the impact of light on cognition.

Moving on from this study, one of my colleagues will investigate the connectivity changes taking place within the hypothalamus as a function of illuminance variations. I choose to focus specifically on the emotional task, as I am interested in understanding the influence light has on emotional processing and mood regulation.

In chapter four, we left the diencephalon and brainstem to focus on a region that could be key to one of the most popular applications of light, light therapy. Light has been proven to influence mood and bright light therapy is considered a treatment or adjunctive therapy for several mood disorders (Penders et al., 2016; Pjrek et al., 2020). The long-term impact of light on mood, as seen in light therapy treatment, cannot be addressed directly using the protocol we have chosen for this study. However, emotion processing and long-term mood changes are very closely related and here we discuss the impact of illuminance on the emotional task of the protocol.

The light-sensitive NIF pathways of the retina are thought to underlie light's influence on mood although the exact mechanism has not been established (Koorengevel et al., 2001; Vandewalle, Hébert, et al., 2011). What is known is that ipRGCs innervate several brain regions involved in mood and emotional regulation, including the amygdala. In rodents, the central and medial amygdala are innervated by ipRGCs (Delwig et al., 2016; Tri & Do, 2019). There is some evidence in rodents, of both brain regions being involved in light influence of fear-related behaviour through ipRGCs (Vinkers et al., 2010; G. Wang et al., 2023).

In humans, the amygdala is known to be very important for mood regulation and emotional processing (Šimić et al., 2021). The amygdala is a complex structure composed of approximately 13 nuclei (Whalen & Phelps, 2009). Previous neuroimaging studies on lights' impact on the amygdala in humans have found conflicting results. An earlier study found that monochromatic blue wavelength light led to enhanced activity in the amygdala, whereas a resting-state fMRI study found that polychromatic white light suppressed activity in the amygdala (McGlashan et al., 2021; Vandewalle et al., 2010).

Understanding the mechanism underlying light's impact on mood will benefit the development of light therapy. Therefore, following on from the previous research, we wanted to investigate if there are regional differences in how the amygdala is influenced by illuminance variations within an emotional context. We hypothesised that for the medial and central nuclei of the amygdala higher illuminance would have a stimulating impact on their activity due to its innervation by ipRGCs. However, we found that the medial and other subparts of the amygdala showed a marked and linear reduction of activity with increasing illuminance specifically when processing emotional stimuli.

Finally, in chapter five, we discuss the main findings of the thesis work and try to integrate them with the existing literature. We re-evaluated some of the limitations of the thesis and, in closing suggest the potential future direction of the research on the NIF impact of light.

Chapter 2

Impact of light on task-evoked pupil responses during cognitive tasks

This chapter is based on our published article in the Journal of Sleep Research:

Campbell, I., Beckers, E., Sharifpour, R., Berger, A., Paparella, I., Balda Aizpurua, J. F., Koshmanova, E., Mortazavi, N., Sherif, S., & Vandewalle, G. (2023). **Impact of light on task-evoked pupil responses during cognitive tasks**. *Journal of Sleep Research e14101.* https://doi.org/10.1111/jsr.14101

Abstract

Light has many non-image-forming functions including modulation of pupil size and stimulation of alertness and cognition. Part of these non-image-forming effects may be mediated by the brainstem locus coeruleus. The processing of sensory inputs can be associated with a transient pupil dilation that is likely driven in part by the phasic activity of the locus coeruleus. In the present study, we aimed to characterise the task-evoked pupil response associated with auditory inputs under different light levels and across two cognitive tasks. We continuously monitored the pupil of 20 young healthy participants (mean [SD] 24.05 [4.0] years; 14 women) whilst they completed an attentional and an emotional auditory task whilst exposed to repeated 30–40-s blocks of light interleaved with darkness periods. Blocks could either consist of monochromatic orange light (0.16 melanopic equivalent daylight illuminance (EDI) lux) or blue-enriched white light of three different levels [37, 92, 190 melanopic EDI lux; 6500 K]. For the analysis, 15 and then 14 participants were included in the attentional and emotional tasks, respectively. Generalised linear mixed models showed a significant main effect of light level on the task-evoked pupil responses triggered by the attentional and emotional tasks ($p \leq 0.0001$). The impact of light was different for the target versus non-target stimulus of the attentional task but was not different for the emotional and neutral stimulus of the emotional task. There is a smaller sustained pupil size during brighter light blocks but, a higher light level triggers a stronger task-evoked pupil response to auditory stimulation, presumably through the recruitment of the locus coeruleus.

Introduction

The non-image-forming (NIF) system (also termed non-visual system) in the human retina detects environmental irradiance to mediate the influences of light on many NIF functions, including circadian entrainment (Berson et al., 2002), melatonin suppression (Brainard et al., 2001), pupillary light responses (Gamlin et al., 2007; Hattar et al., 2002), and stimulation of alertness and cognitive performance (Vandewalle et al., 2009). Light's influence on human alertness and cognition has been reported to be improved by high-intensity white light and short wavelength light, but the impact of light on cognition is complicated by being dependent on several factors, such as time of day, spectral composition, and intensity of the light source (Siraji et al., 2022).

The primary photoreceptors of the NIF system are intrinsically photosensitive retinal ganglion cells (ipRGCs) (Mure, 2021; Provencio et al., 2000), which express the photopigment melanopsin. Animal studies have established that the ipRGCs project to various subcortical brain regions, including the suprachiasmatic nucleus (SCN) of the hypothalamus, the site of the master circadian clock (Tri & Do, 2019). The exact brain pathways involved in light's NIF functions for humans is an area of continued and active research. The locus coeruleus (LC), in the brainstem, receives indirect inputs from the SCN, and it is hypothesised that the LC may be involved in mediating light's influence on alertness and cognition (Aston-Jones et al., 2001; Aston-Jones & Cohen, 2005; Vandewalle et al., 2009). The LC is central to cognition and alertness and a major source of noradrenaline (NA) in the brain (Aston-Jones & Cohen, 2005). A previous neuroimaging study, using a 3-Tesla magnetic resonance imaging (MRI) apparatus reported that an area of the brainstem consistent with the location of the LC is modulated by the wavelength of light whilst performing a non-visual cognitive task (Vandewalle, Schmidt, et al., 2007). The LC is a small bilateral nucleus with a cylinder shape, 15 mm long and 2.5 mm in diameter (50.000 neurons in total), located in the brainstem (Keren et al., 2009). Due to its small size, and its deep location near the fourth ventricle, in vivo imaging of the LC is challenging such that it is difficult to assess its role in mediating the NIF impacts of light in humans. Here, we emphasise that variation in pupil size may be an accessible means to address this research question.

The autonomic nervous system regulates pupil size through the control of two muscles in the pupil, the iris sphincter muscle that causes the constriction of the pupil, and the dilatory muscle that promotes the dilation of the pupil (Larsen & Waters, 2018). Pupil size is dependent on the sympathovagal balance, with parasympathetic activity promoting pupil constriction through recruitment of the iris sphincter muscle via the midbrain Edinger–Westphal nucleus (EWN). Pupil dilation is dependent on the sympathetic system that starts at the hypothalamus and the LC, leading to the inhibition of the activity of the EWN causing pupil dilation through the constriction of the dilator muscle (Larsen & Waters, 2018; Mathôt, 2018). However, pupillary dilation can also be caused by inhibiting the parasympathetic constriction pathway, through LC activity inhibiting the EWN, causing relaxation of the constrictor muscles (Mathôt, 2018; Steinhauer et al., 2015). There is research that suggests that pupil dilation due to cognitive demand is due to inhibition of the parasympathetic pathway (Steinhauer et al., 2004). The interplay between the sympathetic and the parasympathetic systems determines the size of the pupil, with environmental irradiance, mental effort, and fatigue influencing the balance between the two

systems (Larsen & Waters, 2018; Steinhauer et al., 2004; Y. Wang et al., 2018). Change in pupil size can be described as a baseline response where pupil size is maintained for a longer period of time or a faster phasic response (Beatty, 1982).

There is evidence to suggest that fluctuations in pupil size is a proxy measure of the changes in brain arousal during cognitive activity. Specifically, the LC is proposed to be an important region in the control of pupil dilation and changes in pupil diameter have been hypothesised to be a readout of the activity of the NA neurons of the LC (Costa & Rudebeck, 2016; Joshi & Gold, 2020). The LC-NA system has two different modes, baseline tonic activity where there is continuous spiking, and phasic activity, characterised by brief bursts of high-frequency activity that can be spontaneous or in response to salient stimuli (Aston-Jones & Cohen, 2005). Evidence for the link between the LC and pupil size comes from the observation that the neuronal activity of the LC fluctuates almost simultaneously with changes in pupil diameter (Aston-Jones & Cohen, 2005). Further direct evidence comes from research showing that the spiking activity of the LC and the diameter of the pupil were also correlated during a decision-making task in monkeys (Varazzani et al., 2015). Also, spontaneous LC activity correlated with pupil size in monkeys performing a simple fixation task and an evoked pupil dilation occurred when the LC was electrically microstimulated. In addition, other brain areas (inferior colliculus, superior colliculus, anterior and posterior cingulate cortex) also show a less reliable association between pupil size and spontaneous LC activity, suggesting there is co-ordinated neuronal activity in brain areas through LC-mediated arousal (Aston-Jones & Cohen, 2005; Joshi et al., 2016; Nassar et al., 2012). The propagation of LC signal is slow to brain areas due to having unmyelinated projections (Aston-Jones et al., 1985). Furthermore, human studies combining functional MRI (fMRI) and pupillometry have found activations in the area of the brainstem compatible with the LC were linked to fluctuations in pupil diameter, during resting state and for a novelty detection task (de Gee et al., 2017; Murphy et al., 2014). The research highlights that changes in pupil diameter are a relatively reliable means to assess LC activity.

Changes in pupil diameter can also be induced in response to cognitive effort which can be triggered by external stimuli (Joshi & Gold, 2020; Mathôt, 2018). In response to an external task event, the pupil dilates and then constricts back to baseline. This pupil response to a task event is called the 'task-evoked pupil response' (TEPR). These TEPRs can also be influenced by factors such as the demand of the cognitive task and the performance (Aston-Jones & Cohen, 2005; Kahneman & Beatty, 1966). The exact mechanism of the link between the size of the pupil and the activity of the LC is still not known. However, studying TEPRs is nevertheless often considered a non-invasive means to determine the ongoing alterations in the LC phasic activity or arousal level during cognitive tasks.

The pupil is well known to adapt to changes in the light environment, with the pupil constricting at higher light levels mainly driven by the parasympathetic system and dilation mainly being driven by the sympathetic system in darkness (Joshi & Gold, 2020; Larsen & Waters, 2018). This light-induced constriction is maintained by ipRGCs, which innervate the pretectal olivary nucleus, which in turn project to the EWN leading to pupil constriction by parasympathetic drive (Joshi & Gold, 2020). However, whether the TEPRs are influenced by light's NIF effects is currently not known. We, therefore, decided to study the TEPRs under different light conditions. We measured pupil diameter during two cognitive tasks and examined the effect of light level, expressed in

melanopic (mel) equivalent daytime illuminance (EDI) lux, on the TEPRs to auditory stimuli. We hypothesised that the TEPRs would be greater under higher irradiance levels due to the stimulating NIF impact of light, potentially due to an increase in either sympathetic or parasympathetic drive. To test this hypothesis, we used eye tracking data from healthy young participants, who completed an attentional and an emotional auditory cognitive task during a fMRI recording whilst exposed to different light conditions.

Methods

Participants

A total of 20 healthy participants (mean [SD] age 24.05 [4.0] years; 14 women) gave their written informed consent to take part in the study, which was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. The participants were assessed for the exclusion criteria with a semi-structured interview and questionnaires. None of the participants had a history of psychiatric and neurological disorders, sleep disorders, the use of psychoactive drugs or addiction. Participants had no history of night shift work during the last year or recent transmeridian travel during the last 2 months; excessive caffeine (>4 caffeine units/day) or alcohol consumption (>14 alcohol units/week); and were not taking medication or smoking. Their scores on the 21-item Beck Anxiety Inventory (Beck, Steer, et al., 1988) and the Beck Depression Inventory-II (Beck, Epstein, et al., 1988) were mild or minimal (<17), and minimal (<14), respectively normal. Participants reported no history of ophthalmic disorders or auditory impairments and were screened for colour blindness. Due to technical issues (see below), 15 and 14 participants were, respectively, included in the analyses of the attentional and emotional tasks (**Table 2-1**).

Participants followed a loose sleep–wake schedule (±1 h from habitual bedtime/wake-up time) during the 7 days preceding the laboratory experiment to maintain realistic entrained life conditions and avoid excessive sleep restriction across all participants. Sleep–wake schedules were verified using wrist actigraphy and sleep diaries. They were asked to refrain from caffeinated and alcohol-containing beverages and excessive exercise for at least 3 days before the experiment. Participants were familiarised with the MRI environment 1 week before the experiment during an MRI session where structural images of the brain were acquired.

Table 2-1. Table of participants included in the analysis.

	Total Participants	Oddball Analysis	Emotional Analysis
Number of Participants	20	15	14
Age	24.05 (±4.00)	24.33 (±4.15)	24.07 (±4.41)
Sex (M)	6	5	4
Mood (BDI-II)	6.94 (±5.57)	6.0 (±4.78)	6.83 (±6.01)
Anxiety (BAI)	6.55 (±5.98)	5.71 (±4.06)	7.66 (±6.71)
Sleep quality (PSQI)	4.27 (±2.88)	3.78 (±1.92)	4.41(±3.31)
Seasonality (SPAQ)	1.05 (±0.80)	1 (±0.78)	1.16 (±0.83)
Chronotype (HO)	48.5 (±9.26)	47.42 (±9.72)	47.58 (±6.98)
Daytime sleepiness (ESS)	6.27 (±3.21)	6.35 (±2.79)	6.75 (±3.57)
Years of Education	14.35 (±3.12)	14.84 (±2.47)	13.72 (±3.40)

Note: columns for total number of participants who completed the study, and the number of participants included for each task. Refer to the main text for references. Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; HO, Horne and Östberg questionnaire; PSQI, Pittsburgh Sleep Quality Index; SPAQ, Seasonal Pattern Assessment Questionnaire.

Experimental protocol

Most participants (N = 17) arrived at the laboratory 1.5–2 h after habitual wake time, whilst a minority (N = three) were admitted to the laboratory 1.5–2 h before habitual bedtime. The study will investigate the effect time of day (morning versus evening) has on light exposure on brain functions and behaviour in the future. For this paper, all results presented are controlled for time-of-day differences. Participants were first exposed for 5 min to a bright white light (1000 lux) and were then maintained in dim light (<10 lux) for 45 min to standardise participant light history before the fMRI session (**Figure 2-1**-A). During this period participants were given instructions about the fMRI cognitive tasks and completed practice tasks. The fMRI session consisted of participants completing an executive task (25 min), an attentional task (15 min), and an emotional task (20 min) (**Figure 2-1**-B,C). Participants always completed the executive task first and then the order of the following two tasks was pseudorandomised. Only the emotional and the attentional tasks are discussed in the present paper as they consisted of a stream of events, where each sound potential triggers a TEPR.

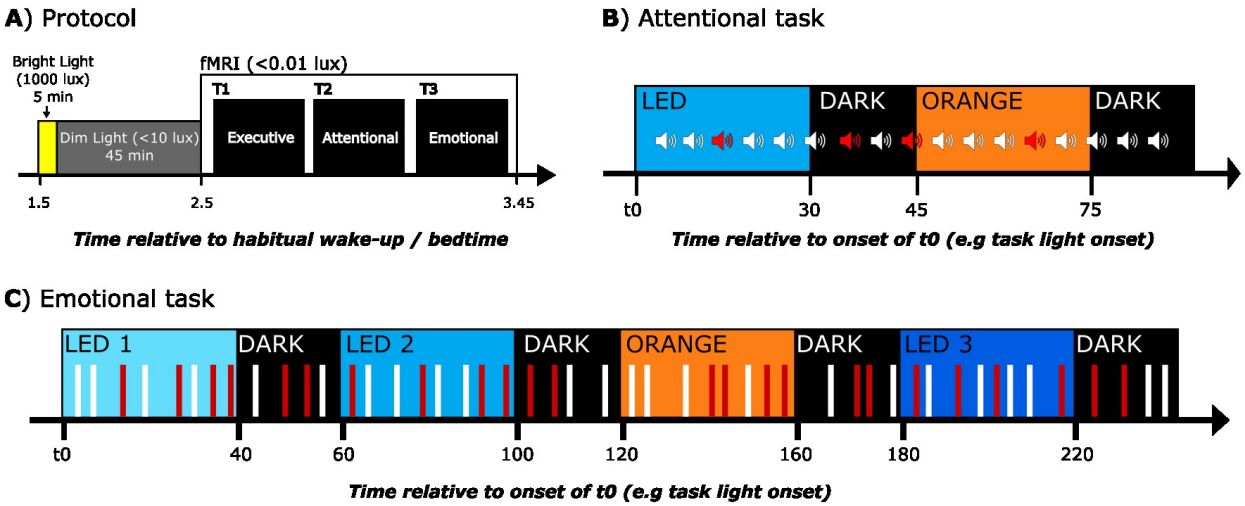


Figure 2-1. Experimental design. (A) General protocol. Time relative to scheduled wake-up/bedtime (h). Following standardisation of immediate prior light exposure (see Methods), participants performed an executive (not discussed in the present paper), an attentional and emotional task in functional magnetic resonance imaging (fMRI). **(B)** Detailed procedures of the attentional task (oddball). Time (s) relative to t0, a time point arbitrarily chosen as the light onset of the session. The task consisted of a stream of standard sounds (80%) and pseudo-randomly interspersed odd sounds (20%); participants were asked to identify the odd stimuli through a button press. Whilst completing the task participants were exposed to blue-enriched white light (BEL; 92 melanopic [mel] equivalent daylight illuminance [EDI] lux; 6500 K) (MID) and a monochromatic orange (0.16 mel EDI lux; 589mn) light. Light exposures lasted 30 s and were separated by 15-s periods of darkness. Odd (red) and standard (white) stimuli were equally distributed across the two light conditions and darkness. **(C)** Detailed procedures of the emotional task. Time (s) relative to t0, a time point arbitrarily chosen as the light onset of the session. The task consisted of a lure gender discrimination of auditory vocalisations of the three pseudo-word types ('goster', 'niuvenci', or 'figotleich') whilst exposed to the alternating white BEL of three different intensities (37, 92, 190 mel EDI lux; 6500 K) (LOW, MID, HIGH) and a monochromatic orange (0.16 mel EDI lux; 589mn) light. Light exposures lasted 30–40 s and were separated by 15–20-s periods of darkness. Untold to the participants, vocalisations were pronounced with angry (red bars) and neutral (white bars) prosody pseudo-randomly and equally distributed across the three light conditions.

An MRI-compatible light system (**Appendix 1. Suppl Figure 6-1**) designed-in-laboratory was developed to ensure relatively uniform and indirect illumination of participants' eyes whilst in the MRI scanner. An 8-m long MRI-compatible dual-branched optic fibre (Setra Systems, MA, USA) transmitted light from a light box (SugarCUBE, Ushio America, CA, USA), that was stored in the MRI control room. The dual end of the optic fibre was attached to a light stand fitted at the back of the MRI coil. This allowed for equal illumination of the participants' eyes. A filter wheel (Spectral Products, AB300, NM, USA) and optical fibre filters (a monochromatic orange light filter [589mn; full width at half maximum: 10 nm] and a UV long bypass [433–1650 nm] filter) were used to create the light conditions needed for the experiment. Participants were asked to keep their eyes open and try not to blink too much during the cognitive tasks.

Both tasks were programmed with Opensesame (3.2.8) (Mathôt et al., 2012) and launched from a computer in the MRI control room. Participants heard the auditory stimuli through MR-compatible headphones (Sensimetrics, Malden, MA) and the volume was set by the participant before starting the tasks to ensure a good auditory perception of all the task stimuli. Participants used an MRI-compatible button box to respond to task items (Current Designs, Philadelphia, PA, USA). During the attentional task, participants were exposed to 30 s of light blocks separated by 15 s of darkness (<0.1 lux). The spectra of the lights were assessed at the level of the end of the optic fibre (AvaSpec-2048, Avantes, The Netherlands). Irradiance could not be measured directly in the magnet, but the light source was calibrated (840-C power meter, Newport, Irvine, CA, USA). The light conditions used were a polychromatic, blue-enriched white light emitting diode (LED) light (92 mel EDI lux; 6500 K) and a monochromatic orange light (0.16 mel EDI lux). The light blocks were repeated seven times for each light condition. During the emotional task, participants were exposed to 30–40-s periods of light blocks separated by 20 s of darkness (<0.1 lux). The light conditions used were three different irradiances of a polychromatic, blue-enriched white LED light (37, 92, 190 mel EDI lux; 6500 K) and a monochromatic orange light (0.16 mel EDI lux) (**Figure 2-2**; **Table 2-2**). The light blocks were repeated five times for each light condition.

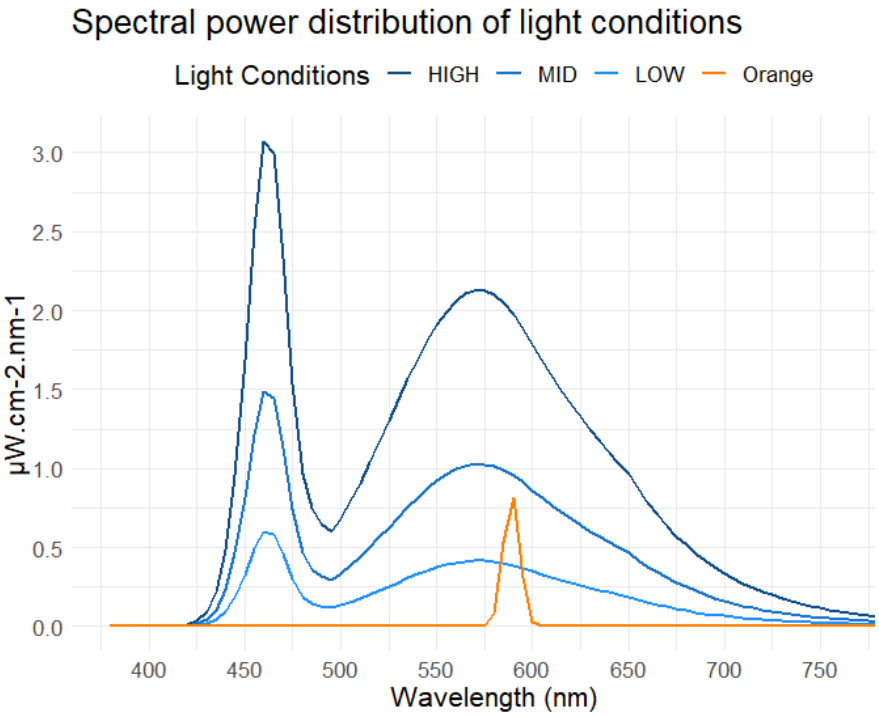


Figure 2-2. Spectral power distribution of light conditions. Orange: monochromatic orange light, 0.16 melanopic (mel) equivalent daylight illuminance (EDI) lux, 589 mn; blue-enriched white light (BEL) LOW, MID, and HIGH: light of three different intensities (37, 92, 190 mel EDI lux; 6500 K). See **Table 2-2** for additional characteristics.

Attentional Task

The attentional task used was a mismatch negativity or oddball task (Kiehl & Liddle, 2003). Participants were asked to detect a rare randomly occurring target (or odd) item in a stream of frequent standard items. They used the keypad to report the detection of the odd items. Stimuli (n = 315) consisted of frequent standard (500 Hz, 100 ms) and odd tones (1000 Hz, 100 ms), presented 80% and 20% of the time, respectively, in a pseudo-randomised order. The interstimulus interval between stimuli was 2 s. Target and standard stimuli were equally distributed across the two light conditions and the separating darkness periods (**Figure 2-1**-B). The instruction was to prioritise accuracy over rapidity when responding.

Emotional Task

The emotional task used was a gender discrimination of auditory vocalisations task (Banse & Scherer, 1996). Participants were asked to use the keypad to indicate what they believed the gender of the person pronouncing each token was. The gender classification was a lure task ensuring participants paid attention to the auditory stimulation. The purpose of the task was to trigger an emotional response as participants were not told that 50% of the stimuli were pronounced with angry prosodies. The 240 auditory stimuli were pronounced by professional actors (50% women) and consisted of three meaningless words ('goster', 'niuvenci', 'figotleich'). The stimuli were expressed in either an angry or neutral prosody, which has been validated by behavioural assessments (Banse & Scherer, 1996) and in previous experiments (Grandjean et al., 2005; Sander et al., 2005). The stimuli were also matched for the duration (750 ms) and mean acoustic energy to avoid loudness effects. During each 30–40-s light block, four angry prosody stimuli and four neutral prosody stimuli were presented in a pseudo-random order and delivered every 3–5 s. A total of 160 distinct voice stimuli (50% angry; 50% neutral) were distributed across the four light conditions. The darkness period separating each light block contained two angry and two neutral stimuli. A total of 80 distinct voice stimuli (50% angry; 50% neutral) were distributed across the darkness periods (**Figure 2-1**-C). Again, the instruction was to prioritise accuracy over rapidity when responding.

Pupil

The right eye movements and the pupillary size were recorded continuously with an infrared eye tracking system (Eyelink-1000, SR Research, Osgoode, ON, Canada; sampling rate, 1000 Hz). Pupil data were analysed using MATLAB R2019b (MathWorks, Natick, MA, USA). Participants with >25% missing or corrupted eye-tracking data were excluded. Blink events were replaced with linear interpolation and the data were smoothed using the 'rlowess' a robust linear regression function. The total amount of interpolated data included was 21% ± 9% and 22% ± 9% for the attentional and the emotional task, respectively. The transient pupil response was computed as

the change in the pupil diameter from before (baseline) and after (maximum) the auditory stimulus presentation. Baseline pupil diameter was computed as the mean pupil diameter over 1 s before stimuli onset. The maximum pupil diameter was defined as the maximum value over a 1.5 s window following sound onset. TEPRs were computed as the ratio between maximum and baseline diameter. For the attentional task, one participant was excluded because they did not complete the entire attentional task and four were excluded as there was >25% missing or corrupt pupil data. Therefore, we included 15 participants in the analysis of the oddball task (**Table 2-1**). For the emotional task, two participants were excluded as there was >25% missing or corrupt pupil data. One participant was excluded because he did not complete the entire emotional task correctly and three were excluded due to problems with the eye-tracking system. Therefore, we included 14 participants in the analysis of the emotional task (**Table 2-1**).

Statistical analyses

Statistical analyses were computed using the Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC, USA) using individual TEPRs segregated per stimulus type and light condition. Values were considered outliers if they were > ± 3 standard deviations (SDs) across the entire dataset and were therefore removed. Analyses consisted of generalised linear mixed models (GLMM) seeking effects of light condition (i.e., mel EDI lux level) on the TEPRs. TEPRs were set as the dependent variable, with subject as a random factor (intercept), and light condition and stimulus type as repeated measures (autoregressive (1) correlation), together with the time of day, age, body mass index and sex as covariates. GLMM were adjusted for the dependent variable distribution. Post hoc contrasts were corrected for multiple comparisons using a Tukey adjustment.

Table 2-2. Light characteristics.

	Low BEL	Mid BEL	High BEL	Monochromatic light (589nm)
Photopic illuminance (lux)	47	116	240	7.5
Peak Spectral Irradiance (nm)	460	460	460	590
Melanopic EDI lux (ipRGCs)	37	92	190	0.16
Rhodopic EDI lux (Rods)	39	97	201	0.94
Cyanopic EDI lux (S-cones)	32	79	163	0
Chloropic EDI lux (M-cones)	44	110	227	5
Erythropic EDI lux (L-cones)	46	113	233	8
Irradiance ($\mu W/cm^2$)	15	36	75	1.4
Photon flux($1/cm^2/s$)	4.12E+13	1.02E+14	2.10E+14	4.24E+12
Log Photon Flux (log_{10} ($1/cm^2/s$)	13.61	14.01	14.32	12.63
Narrowband peak	-	-	-	589
Narrowband FWHM	-	-	-	10

Note: additional light characteristics of the two light sources used. Blue-enriched white light (BEL) (low, mid, and high) and monochromatic light (589 nm). Abbreviations: EDI, equivalent daylight illuminance; FWHM, full width at half-maximum; ipRGCs, intrinsically photosensitive retinal ganglion cells.

Results

The performance of both tasks was high, with a mean (SD) 96.6% (0.5%) of detection of target sounds during the attentional (oddball) task and 93.9% (7.21%) button response during the emotional (gender classification) task. In line with the literature (Sander et al., 2005; Vandewalle et al., 2010), for the emotional task, reaction times (RTs) were faster for neutral stimuli with a mean (SD) of 1192 (182.8) ms compared to 1234 (199.8) ms RT for emotional prosody vocal stimulation ($p = 0.0004$) suggesting that the task was successful in triggering a differential response according to the emotional content. As no response was collected for the standard tone in the oddball task, RT could not be compared between stimulus types for the attentional task. Although not relevant to the task and not compromising any emotional effect (Grandjean et al., 2005), gender detection accuracy for the emotional task (mean [SD] 79% [11%]) was slightly lower than what has previously been reported for the task (Sander et al., 2005). For both tasks, there were no significant main effects of the light level on RTs ($F < 2.1$, $p \geq 0.1$) and accuracy ($F < 2.1$, $p \geq 0.1$), and there was no light exposure by stimulus type interaction for the emotional task ($F_{[4,34.04]} = 0.25$, $p = 0.9$). This was expected, as behavioural performance differences unspecific to light exposure would significantly bias neuroimaging results (Paparella et al., 2023).

It is well established that pupil size changes in response to variations in environmental irradiance. In a joint paper (Beckers et al., 2023), we notably confirmed this and reported that the sustained

constriction of the pupil increased with higher light levels in the same sample of participants who completed the same protocol. In contrast to the joint paper (Beckers et al., 2023), here, we consider whether changes in light conditions, as indexed by mel EDI lux, impact the TEPRs for an attentional and emotional task. Both tasks consist of streams of events that putatively trigger TEPRs, and both have two types of auditory stimulations. We hypothesised that the TEPRs would be greater under higher light levels due to the stimulating NIF impact of light.

To characterise the effect of light conditions on TEPRs for the attentional task, an initial GLMM was conducted with TEPRs during the oddball task as the dependent variable. The results yielded significant main effects of stimulus type (target and standard tones; $F_{[1,1548]} = 189.27$, $p \leq 0.0001$) and light condition ($F_{[2,1548]} = 13.71$, $p \leq 0.0001$). Importantly, the GLMM detected a significant interaction between stimulus type and light condition ($F_{[2,1548]} = 3.65$, $p = 0.02$) (**Figure 2-3**-A). Post hoc analyses first indicated that TEPRs were larger for target versus standard stimuli ($p \leq 0.0001$). They further indicated that TEPRs were smaller during darkness as compared to the blue-enriched white light condition (92 mel EDI lux; $p \leq 0.0001$) but TEPRs during darkness were not significantly different when compared to the orange (0.16 mel EDI lux; $p = 0.1$) light condition. However, TEPRs were significantly larger under the blue-enriched white light (92 mel EDI lux; $p = 0.002$) when compared to the orange light (0.16 mel EDI lux). Finally, post hoc analyses indicated that TEPRs significantly increased with higher light irradiance for the standard ($p \leq 0.0001$) but not the target stimuli ($p > 0.2$).

The second GLMM, with TEPRs during the emotional task as the dependent variable, led to a significant main effect of light condition ($F_{[4,1072]} = 77.78$, $p \leq 0.0001$). Despite there being a qualitative difference between angry and neutral stimuli, there was no significant main effect of stimulus type ($F_{[1,1072]} = 0.06$, $p = 0.8$) (**Figure 2-3**-B). In addition, there was no interaction between stimulus type and light condition ($F_{[4,1073]} = 0.5$, $p = 0.7$). Post hoc analysis showed a significant difference between darkness and all four light conditions ($p \leq 0.0001$), as well as between the orange (0.16 mel EDI lux) light and the blue-enriched white light conditions (37, 92, 190 mel EDI lux; $p \leq 0.0001$). There was no significant difference between the blue-enriched white light conditions (37, 92, 190 mel EDI lux; $p \geq 0.7$).

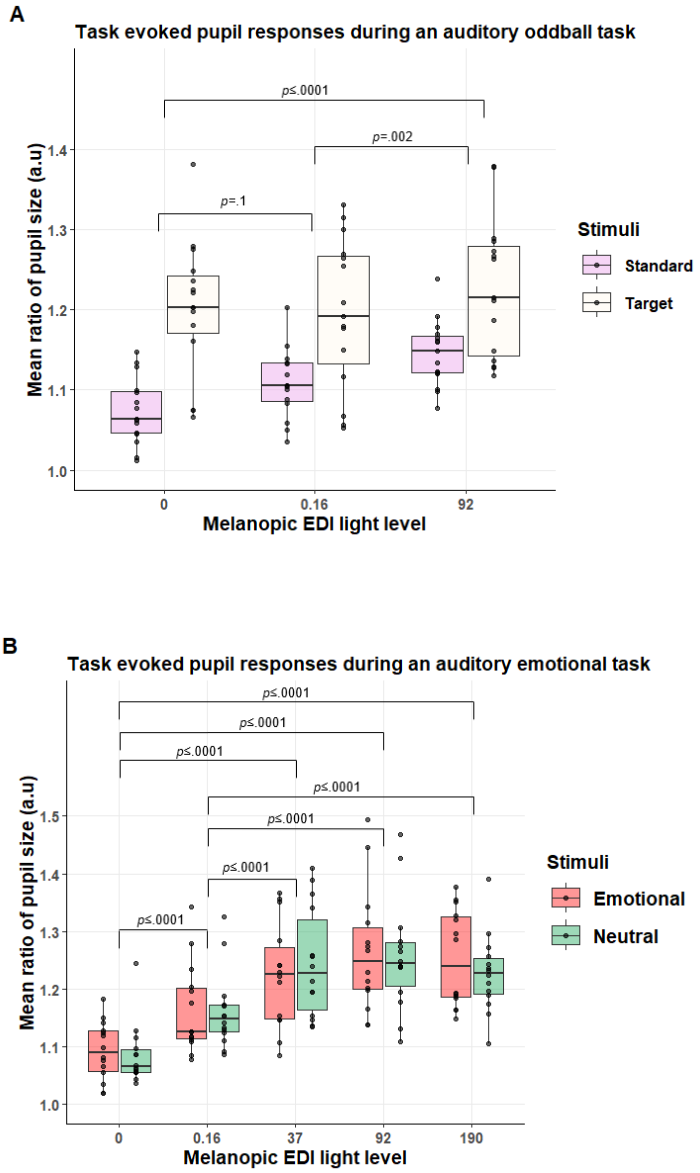


Figure 2-3. Task-evoked pupil response (TEPRs) across light conditions and stimulus type. (A) TEPRs under the different light conditions during the attentional (oddball) task (N = 15; mean [SD] age 24.33 [4.15] years; 10 women). Individual average TEPRs were computed per stimulus type and light condition. TEPRs were significantly higher for target versus standard stimulations ($p < 0.0001$), as well as under higher versus lower melanopic equivalent daylight illuminance (EDI) light levels ($p < 0.0001$). A significant light condition by stimulus type was also found ($p = 0.02$) and post hoc analyses indicated that TEPRs significantly increased with higher light irradiance for the standard but not the target stimulations. **(B)** TEPRs under different light levels during the emotional task (N = 14; mean [SD] age 24.0 [4.41] years; 10 women). Individual average TEPRs were computed per stimulus type and light condition. There was no significant difference between neutral and emotional stimulations ($p = 0.8$) whilst TEPRs were greater under higher versus lower melanopic light levels ($p < 0.0001$). There was no light condition by stimulus type interaction ($p = 0.7$).

Discussion

The TEPRs consist of transient pupil dilations triggered by the processing of stimulations over diverse cognitive domains. They are considered to be at least in part driven by a transient increase in the phasic activity of the LC-NA system and potentially other brain areas (Joshi et al., 2016; Larsen & Waters, 2018). In the present study, we tested whether the TEPRs evoked by auditory stimulus during two cognitive tasks would be larger under higher ambient light levels, when the parasympathetic drive to the pupil is high, to investigate whether light's NIF impacts on cognitive brain activity could potentially be mediated through the LC. To test this hypothesis, we analysed eye tracking data from young healthy participants who completed an attentional and an emotional cognitive task during an fMRI protocol whilst exposed to different light conditions. The results reveal that when there is a smaller sustained pupil size at higher light levels (Beckers et al., 2023), the TEPRs to auditory stimulus were larger under higher light irradiances, as indexed by mel EDI lux. Although this main finding was detected for both the attentional and emotional tasks, we further observed task-specific differences in the impact light irradiance has on the different types of stimuli of each task.

The LC is involved in the processing of salient events through an increase in its phasic activity (Berridge & Waterhouse, 2003). The oddball task, which mimics novelty/salience detection has been previously used to assess the phasic activity of the LC (Rajkowski et al., 1994), whilst the LC is also known to be important for emotional processing (Aston-Jones & Cohen, 2005; Bradley et al., 2008). The oddball task was reported to trigger TEPRs (both in the visual and auditory modality) that were larger for the odd target stimuli, which is in line with our findings (Gilzenrat et al., 2010; Murphy et al., 2014). Similarly, TEPRs were also reported using emotional tasks (Aston-Jones & Cohen, 2005; Bradley et al., 2008). Pupil size depends on the parasympathetic–sympathetic balance and transient pupil dilation is thought to reflect an increase in arousal due to an increase in the sympathetic tone (Larsen & Waters, 2018). Although recent investigations have indicated that it is likely not the sole driver of transient pupil dilation, in vivo animal studies support that transient increases in pupil size were directly related to the firing of the neurons of the LC (Costa & Rudebeck, 2016). Our findings could suggest therefore that the phasic activity of the LC related to an ongoing cognitive process is likely to be affected by changes in ambient light level. Light is known to increase arousal and have wake-promoting effects and can cause the activation of the pupil dilation pathway via the LC, through indirect sympathetic influence by stimulating the SCN, and the dorsomedial hypothalamus (Mathôt, 2018). The LC could also cause pupil dilation via sympathetic drive by its projection to the intermediolateral column and potential through projections to the superior colliculus (Mathôt, 2018; Szabadi, 2018). Alternatively, our results could be interpreted as transient inhibition of the parasympathetic constriction pathway, through EWN inhibition by the LC, leading to an increase in pupil dilation under higher light levels (Steinhauer et al., 2015). Transient inhibition of parasympathetic signal may indeed be the primary pathway involved in pupil dilation caused by arousal and cognition (Steinhauer et al., 2004; Szabadi, 2018).

The LC is a good candidate to mediate the impact of light on human alertness and cognition through an effect on other subcortical and cortical structures (Aston-Jones & Cohen, 2005). The thalamus pulvinar could likely be one of these downstream structures, as it is the most

consistently affected by light in previous investigations on the impact of light on non-visual cognitive brain activity (Vandewalle et al., 2009). Other structures and nuclei, e.g., within the hypothalamus or basal forebrain, could also be implicated, whilst the recruitment of limbic and cortical areas would depend on the ongoing cognitive processes (Gaggioni et al., 2014). Our results indicate that the impact of increasing light level is stronger for standard compared with target stimulation. We interpret this as a ceiling effect for TEPRs elicited by target stimulations that cannot be further increased, whilst the milder TEPRs triggered by standard stimulations in darkness or at lower light levels can continue to be increased under higher ambient light. In line with this interpretation, the impact of light on non-visual cognitive brain activity was previously found to be reduced in the evening during the wake-maintenance zone, when the endogenous circadian signal promoting wakefulness is strong and therefore when alertness could not be further increased by lights influence (Vandewalle, Archer, et al., 2011). In contrast, light's impact was increased in the morning following sleep deprivation, when the circadian signal is weaker but the need for sleep is high due to sleep loss. Therefore, alertness can benefit from the external stimulating impact of light (Vandewalle, Archer, et al., 2011). If our interpretation is correct, this could mean that light can only affect the activity of the LC when it is not already highly recruited by the processing of a salient stimulation. Even though the average TEPR to target stimuli remains stable across light conditions, the variance of TEPR was larger for target stimuli. We cannot rule out that it contributed to the absence of difference between light conditions for target stimuli.

The situation is different if we consider the emotional task as we find no difference between the TEPRs triggered by the emotional and neutral simulations. This could call into question the emotional valence of the stimuli included in the task. However, the emotional task has been previously extensively validated and was successful in triggering differential brain responses to emotional versus neutral stimulations, including in studies interested in the NIF effects of light (Banse & Scherer, 1996; Grandjean et al., 2005; Vandewalle et al., 2010). We also find that RTs were significantly slower in response to emotional versus neutral stimulations, which is in line with the literature and supports that the emotional valence of the stimuli was perceived by the participants (Sander et al., 2005; Vandewalle et al., 2010). Yet, the emotional response may not be strong and/or different enough from the response to neutral stimuli to be detected with 15 subjects. Auditory emotional stimuli are indeed considered to be less effective at provoking an emotional response when compared to visual emotional stimuli (Bradley et al., 2008). It may also be that the unexpected occurrence of neutral stimulations (stimulations were pseudo-randomly delivered every 3– 5 s) triggers a TEPR that is similar to the emotional stimuli. Our results further indicate that given the relatively mild response elicited in darkness or at lower light levels, TEPRs could be increased by increasing light levels. The maximum increase seems to be reached already with the lower level of polychromatic, blue-enriched white light (37 mel EDI lux) to ceiling thereafter. Interestingly, the maximum TEPRs for both the oddball and emotional tasks seem to lay on average around 1.25, i.e., a 25% increase on average in pupil size compared to baseline (cf. **Figure 2-3**).

Study Limitations

We emphasise that our study has limitations. The light conditions included do not allow for determining which of the human photoreceptors are mostly contributing to the TEPRs. Rods, cones, and ipRGCs could equally be involved with differential recruitment at the different light levels we used (Mure, 2021). Future research could use metameric light sources with which the wavelength compositions can be manipulated to differentially recruit one photoreceptor type whilst leaving the others relatively similarly recruited (Viénot et al., 2012). We are also unable to say conclusively to what extent the sympathetic and/or parasympathetic system contributes to the increase in TEPRs under higher light levels. The LC is considered the centre point of the NA pupil control pathway and contains sympathetic and parasympathetic premotor neurons (Szabadi, 2018). Yet other nuclei may affect pupil size and TEPRs and contribute to our results (Joshi et al., 2016). We stress that we did not have access to the brain activity associated with TEPRs. The assumptions made regarding the recruitment of the LC can only be verified using the fMRI data acquired simultaneously with the pupil data. Further research using drugs that lead to the alteration of pupil size control, through the modification of the activity/transmission of the sympathetic or parasympathetic NA s may elucidate the contribution of sympathetic or parasympathetic systems to increase in TEPRs under higher light levels (Steinhauer et al., 2015). Finally, during a goal-oriented task, the phasic activity of the LC facilitates task-related behaviours to optimise performance, and tonic activity is involved in task disengagement and search for alternative behaviours. Switching between these two modes allows to maximise utility (Aston-Jones & Cohen, 2005). Therefore, it can be hypothesised that we only investigated the phasic activity of the LC, as both tasks used in the study are stream-of-conscious tasks and do not involve the exploration of alternative behaviours at the cost of task performance. However, we cannot rule out the possibility of tonic activity affecting the results.

Conclusion

Overall, this study shows that the NIF impacts of light can be detected when focusing on pupil size with transient pupil dilation induced by increasing light levels. This is true for two different auditory cognitive tasks whilst increased transient pupil dilation may only be possible if TEPRs are not already at maximum. Future research is needed to conclude if it is the sympathetic or parasympathetic drive that is causing the increase in TEPRs under higher light levels. There is a putative link between LC phasic activity and transient pupil dilation (Costa & Rudebeck, 2016), alternatively, transient pupil dilation may be due to the transient inhibition of the parasympathetic signal (Steinhauer et al., 2015). The results presented here provide further support for the involvement of the LC in the stimulating impact of light on alertness and cognition.

Chapter 3

Regional response to light illuminance across the human hypothalamus

This chapter is based on our submitted article:

Campbell, I., Sharifpour, R., Balda Aizpurua, J. F., Beckers, E., Paparella, I., Berger, A., Berger, A., Mortazavi, N., Read, J., Zubkov, M., Talwar, P., Collette, F., Sherif, S., Phillips, C., Lamalle, L., & Vandewalle, G. (2023). **Regional response to light illuminance across the human hypothalamus.** *Submitted.*

Abstract

Light exerts multiple non-image-forming biological effects on physiology including the stimulation of alertness and cognition. However, the subcortical circuitry underlying the stimulating impact of light is not established in humans. We used 7 Tesla functional magnetic resonance imaging to assess the impact of variations in light illuminance on the regional activity of the hypothalamus while healthy young adults (N=26; 16 women; 24.3 40 ± 2.9y) were completing two auditory cognitive tasks. We find that, during both the executive and emotional tasks, higher illuminance triggered an activity increase over the posterior part of the hypothalamus, which includes part of the tuberomamillary nucleus and the posterior part of the lateral hypothalamus. In contrast, increasing illuminance evoked a decrease in activity over the anterior and ventral parts of the hypothalamus, encompassing notably the suprachiasmatic nucleus and another part of the tuberomammillary nucleus. Critically, the performance of the executive task was improved under higher illuminance and was negatively correlated with the activity of the posterior hypothalamus area. These findings reveal the distinct local dynamics of different hypothalamus regions that underlie the impact of light on cognition. They may suggest that light acts on the orexin and histamine system to affect the quality of wakefulness.

Introduction

Light exerts multiple non-image-forming (NIF) biological effects that influence the quality of sleep and wakefulness, and higher illuminance is known to stimulate alertness and cognition (Campbell, Sharifpour, & Vandewalle, 2023). The biological effects of light primarily rely on a subclass of retinal ganglion cells that are intrinsically photosensitive (ipRGCs) because they express the photopigment melanopsin, which is maximally sensitive to photons with wavelength ~480nm. IpRGCs combine the light signalling of rods and cones to their intrinsic photosensitivity and, collectively, the biological effects of light present a maximal sensitivity to the shorter blue wavelength of visible light (Tri & Do, 2019). IpRGCs project to multiple subcortical brain areas and their denser projections are found within the hypothalamus, particularly in nuclei involved in sleep and wakefulness regulation (Scammell et al., 2017; Tri & Do, 2019). The suprachiasmatic nucleus (SCN), which is the site of the principal circadian clock, receives the strongest inputs from ipRGC inputs, over the anterior part of the hypothalamus (Hattar et al., 2006). Other nuclei also receive ipRGC projections: the subparaventricular zone, one of the main output routes of the SCN, the ventrolateral preoptic nucleus (VLPO) and the preoptic nucleus (PON) involved in sleep initiation and also found in the anterior part of the hypothalamus; the lateral hypothalamus (LH), site of the orexinergic wake-promoting neurons and melanin-concentrating hormone sleep-promoting neurons, found in contrast over the lateral and posterior parts of the hypothalamus (Scammell et al., 2017; Tri & Do, 2019).

The brain circuitry underlying the biological effects of light has mostly been uncovered in nocturnal rodent models (Campbell, Sharifpour, & Vandewalle, 2023; Tri & Do, 2019). Translation to diurnal human beings, where the later maturation of the cortex allows for complex cognitive processing (Braak & Del Tredici, 2015), remains scarce. In particular, whether hypothalamus nuclei contribute to the stimulating impact of light on cognition in humans is not established.

We addressed this question using ultra-high-field (UHF) 7 Tesla (7T) functional magnetic resonance imaging (fMRI) in healthy young adults exposed to light of various illuminance while engaged in two different auditory cognitive tasks. We find that higher illuminance increased the activity of the posterior part of the hypothalamus encompassing the mamillary bodies (MB) and parts of the LH and tuberomammillary nucleus (TMN). In contrast, higher illuminance decreased the activity over the anterior and ventral parts of the hypothalamus encapsulating notably the SCN and another part of the TMN. Critically, the pattern of modulation was consistent across the two cognitive tasks. Importantly, the performance of the complex cognitive task was improved under higher illuminance while the activity of the posterior part of the hypothalamus was correlated to task performance. The findings reveal the distinct local dynamics of different hypothalamus areas in response to changing illuminance that may contribute to light's impact on cognition.

Methods

The data used in this paper arise from a large study that is leading to several publications and part of the methods have been published previously (Beckers et al., 2023; Campbell, Beckers, et al., 2023; Paparella et al., 2023). The protocol was approved by the Ethics Committee of the Faculty of Medicine at the University of Liège. Participants gave their written informed consent to take part in the study and received monetary compensation for their participation.

Participants

Thirty healthy young adults (19 women; 24.3 ± 2.9 y; **Appendix 2. Suppl Table 6-1**) were included in the analyses. Exclusion criteria were assessed through questionnaires and a semi-structured interview: history of psychiatric and neurological disorders, sleep disorders, use of psychoactive drugs or addiction; history of ophthalmic disorders or auditory impairments; colour blindness; night shift work during the last year or recent trans-meridian travel during the last 2 months; excessive caffeine (>4 caffeine units/day) or alcohol consumption (>14 alcohol units/week); medication affecting the central nervous system; smoking; pregnancy or breast-feeding (women); counter indication for MRI-scanning. All participants had to score < 18 on the 21-item Beck Anxiety Inventory (up to mild anxiety) (Beck, Epstein, et al., 1988), and <14 on the Beck Depression Inventory-II (up to mild depression) (Beck, Steer, et al., 1988), < 12 on the Epworth Sleepiness Scale (Johns, 1993), and < 8 on the Pittsburgh Sleep Quality Index (Buysse et al., 1989). Questionnaires further assessed chronotype with the Horne-Östberg questionnaire (Horne & Ostberg, 1976) and seasonality with the Seasonal Pattern Assessment Questionnaire (Rosenthal & Bradt, 1984), but the latter two questionnaires were not used for the inclusion of the participants.

For each task, 4 datasets were missing or had corrupt data such that 26 participants were included in the analyses of each task (23 participants had valid datasets for both tasks). For the emotional task, two participants' data failed the MRI quality control (QC) check, and the other two participants were excluded as they did not complete the entire task. For the executive task, four of the participants' data failed the MRI QC check. **Appendix 2. Suppl Table 6-2** summarises participants' characteristics respective to each task.

Overall Protocol

Participants completed an MRI session at least one week before the experiment during which structural images of the brain were acquired and which served as habituation to the experimental conditions. Participants maintained a loose sleep-wake schedule (± 1h from the habitual sleep/wake-up time) during the 7 days preceding the fMRI experiment to warrant similar circadian entrainment across participants and avoid excessive sleep loss while maintaining realistic real-life conditions (verified using sleep diaries and wrist actigraphy - AX3

accelerometer, Axivity, United Kingdom). Volunteers were requested to refrain from all caffeine and alcohol-containing beverages, and extreme physical activity for 3 days before participating in the fMRI acquisitions. Data acquisitions took place in Liège, Belgium, between December 2020 and May 2023.

Participants arrived at the laboratory 1.5 to 2h after habitual wake time for the fMRI scan. They were first exposed for 5 min to a bright polychromatic white light (1000 lux) and then maintained in dim light (< 10 lux) for 45 min to standardise the participant's recent light history. During this period participants were given instructions about the fMRI cognitive tasks and completed practice tasks on a luminance-controlled laptop (< 10 lux). The fMRI session consisted of participants completing three auditory cognitive tasks while alternatively maintained in darkness or exposed to light: an executive task (25 min), an emotional task (20 min) and an attentional task (15 min) [**Figure 3-1**-A]. The executive task was always completed first, as it was the most demanding task. The order of the following two tasks was counterbalanced. Because it included only 3 light conditions (see below) instead of 5 for the other two tasks, the attentional task was not included in the present analyses. An eye-tracking system (EyeLink 1000Plus, SR Research, Ottawa, Canada) was monitored for proper eye-opening during all data acquisitions.

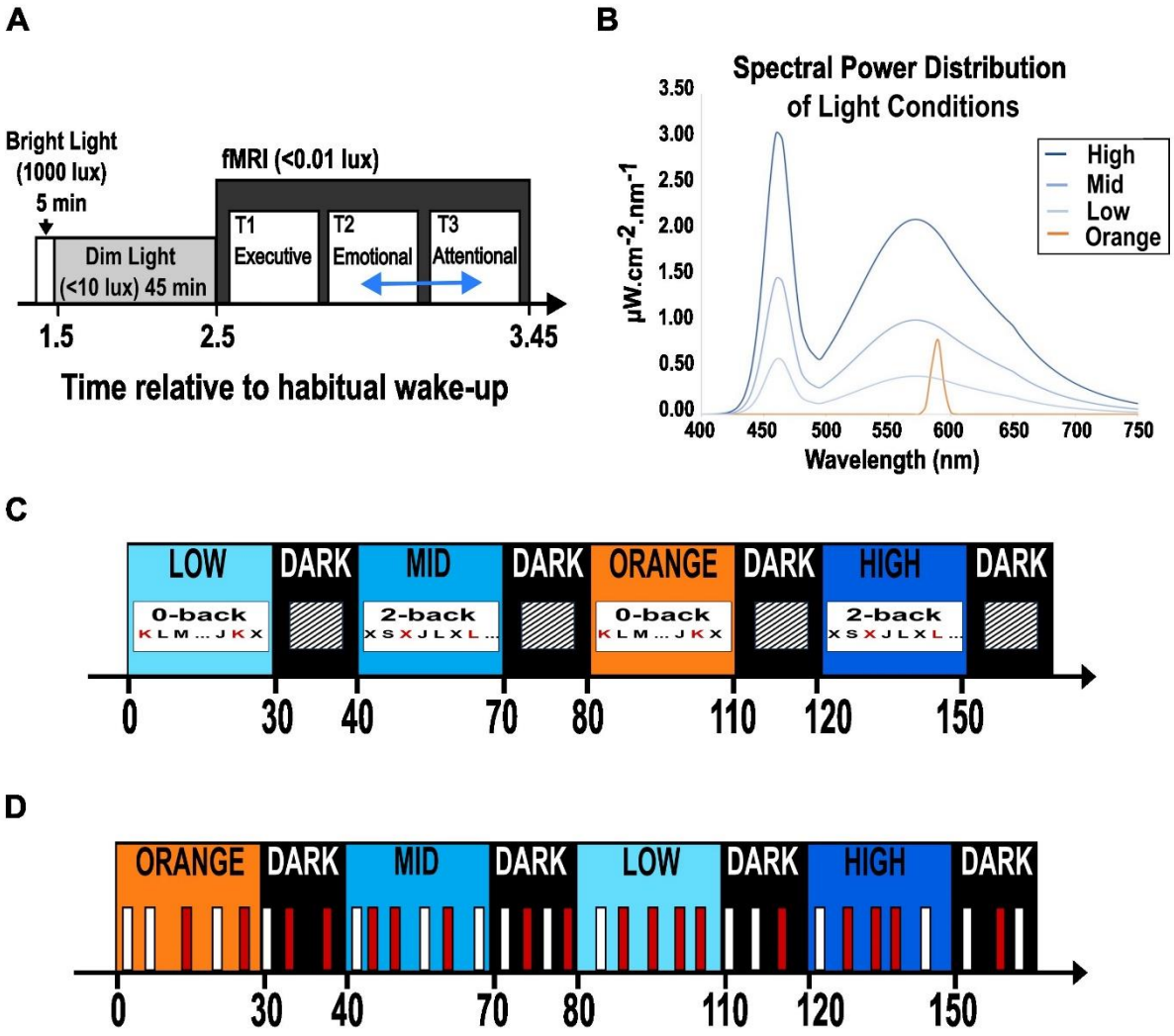


Figure 3-1. Experimental protocol. (A) Overall timeline. After prior light history standardisation, participants performed executive (always first), emotional and attentional tasks (pseudo-randomly 2nd or 3rd, blue arrow). As the attentional task included fewer light conditions, it is not considered in the present manuscript (see methods for more details). **(B)** Spectral power distribution of light exposures. Monochromatic orange: 0.16 mel EDI lux; Polychromatic, blue-enriched light (6500K); LOW, MID, HIGH: 37, 92, 190 mel EDI lux. For the present analyses, we discarded colour differences between the light conditions and only considered illuminance as indexed by mel EDI lux, constituting a limitation of our study. See **Appendix 2. Suppl Table 6-2** for full details). **(C-D)** Tasks procedures. Time is reported in seconds relative to session onset; participants were pseudo-randomly exposed to the 4 light conditions. **(C)** Executive task: alternation of letter detection blocks (0-back) and working memory blocks (2-back). **(D)** Emotional task: lure gender discrimination of vocalizations (50% angry (red), 50% neutral (white).

Light exposure

An 8-m long MRI-compatible optic fibre (1-inch diameter, Setra Systems, MA, USA) transmitted light from a light box (SugarCUBE, Ushio America, CA, USA) to the dual end of the fibre which was attached to a stand fitted at the back of the MRI coil that allowed reproducible fixation and orientation of the optic fibre ends. The dual branches illuminated the inner walls of the head coil to ensure relatively uniform and indirect illumination of participants' eyes. A filter wheel (Spectral Products, AB300, NM, USA) and optical fibre filters (monochromatic narrowband orange filter - 589mn; full width at half maximum: 10 nm - or a UV highpass filter - 433–1650nm) were used to create the light conditions needed for the experiment (see **Figure 3-1**-B **and Appendix 2. Suppl Table 6-2** for in-detail light characteristics).

For the executive and emotional task, the light conditions consisted of three different illuminance of a white, blue-enriched polychromatic LED light (37, 92, 190 mel EDI lux; 6500K) and one illuminance level of monochromatic orange light (.16 mel EDI lux; 590nm full width at half maximum - FWHM: 10 nm). For the present analyses, we discarded colour differences between the light conditions and only considered illuminance as indexed by mel EDI lux, constituting a limitation of our study. In the executive task, participants were exposed to 30s to 70s (median 30s) of light blocks separated by 10s of darkness (< 0.1 lux) and the light blocks were repeated 11 times for each light condition. For the emotional task, participants were exposed to 30 to 40s (median 35s) light blocks separated by 20s of darkness (< 0.1 lux) and the light blocks were repeated five times for each light condition.

The attentional task only included a single illuminance level of the blue-enriched polychromatic LED light (92 mel EDI lux) and one illuminance level of the monochromatic orange light (.16 mel EDI lux), otherwise, the task would have been too long (> 30 min). Participants were exposed to 30s of light blocks separated by 10s of darkness (<0.1 lux). The light blocks were repeated 7 times for each light condition. As mentioned above it is not considered for the present analyses.

Auditory cognitive tasks. The tasks were programmed with Opensesame (3.2.8) (Mathôt et al., 2012). Participants heard the auditory stimuli through MR-compatible earbuds (Sensimetrics, Malden, MA). Before starting the tasks, to ensure optimal auditory perception of task stimuli, participants set the volume through a volume check procedure. Participants used an MRI-compatible keypad to respond to task items (Current Designs, Philadelphia, PA), which was placed in the participant's dominant hand. The tasks were separated by about 5 minutes in near darkness, to recalibrate the eye tracking system and to clarify instructions about the next task to the participant.

Executive Task

The task consisted of an auditory variant of the n-back task (Collette et al., 2005) with a working memory 2-back task and a control letter detection 0-back task. Participants were either asked to detect whether the current item was identical to the letter presented 2 items earlier (2-back) or whether the current item consisted of the letter "K" (0-back) or using the keypad (one button

for “yes”, one button for “no”). A block design was used for this task in which each block included 15 items and lasted 30s. Task blocks were separated by 10-20s rest periods and were preceded by an auditory instruction (500 ms) indicating the type of task to be completed. Task levels were pseudo-randomised across the 4 light conditions with 3 blocks of 0-back and 4 blocks of 2-back per light condition (see **Figure 3-1**-C).

Emotional Task

The task consisted of gender discrimination of auditory vocalizations that were either pronounced with emotional or neutral prosody (Grandjean et al., 2005). Participants were asked to use the keypad to indicate what they believed the gender of the person pronouncing each token was. The gender classification was a lure task ensuring participants paid attention to the auditory stimulation. The purpose of the task was to trigger an emotional response as participants were not told that part of the stimuli was pronounced with angry prosodies. The 240 auditory stimuli were pronounced by professional actors (50% women) and consisted of three meaningless words (“goster”, “niuvenci”, “figotleich”). The stimuli were expressed in either an angry or neutral prosody, which has been validated by behavioural assessments (Banse & Scherer, 1996) and in previous experiments (Grandjean et al., 2005; Sander et al., 2005; Vandewalle et al., 2010). The stimuli were also matched for the duration (750 ms) and mean acoustic energy to avoid loudness effects. During each 30 to 40-s light block, four angry prosody stimuli and four neutral prosody stimuli were presented in a pseudorandom order and delivered every 3 to 5 seconds. A total of 160 distinct voice stimuli (50% angry; 50% neutral) were distributed across the four light conditions. The darkness period separating each light block contained two angry and two neutral stimuli. A total of 80 distinct voice stimuli (50% angry; 50% neutral) were distributed across the darkness periods [see **Figure 3-1**-D].

Data acquisition

The MRI data were acquired in a 7T MAGNETOM Terra MR scanner (Siemens Healthineers, Erlangen, Germany) with a 32-channel receive and 1-channel transmit head coil (Nova Medical, Wilmington, MA, USA). Dielectric pads (Multiwave Imaging, Marseille, France) were placed between the subject’s head and receiver coil to homogenize the magnetic field of Radio Frequency (RF) pulses.

Multislice T2*-weighted fMRI images were obtained with a multi-band Gradient-Recalled Echo - Echo-Planar Imaging (GRE-EPI) sequence using axial slice orientation (TR = 2340 ms, TE = 24 ms, FA = 90°, no interslice gap, in-plane FoV = 224 mm × 224 mm, matrix size = 160 × 160 × 86, voxel size = 1.4 × 1.4 × 1.4 mm^3). To avoid saturation effects, the first three scans were discarded. To correct for physiological noise in the fMRI data the participants’ pulse and respiration movements were recorded using a pulse oximeter and a breathing belt (Siemens Healthineers, Erlangen, Germany). Following the fMRI acquisition a 2D GRE field mapping sequence to assess B0 magnetic field inhomogeneities with the following parameters: TR = 5.2 ms, TEs = 2.26 ms

and 3.28 ms, FA = 15°, bandwidth = 737 Hz/pixel, matrix size = 96 × 128, 96 axial slices, voxel size = (2x2x2) mm^3, acquisition time = 1:38 min, was applied.

For the anatomical image, a high-resolution T1-weighted image was acquired using a Magnetization-Prepared with 2 RApid Gradient Echoes (MP2RAGE) sequence: TR = 4300 ms, TE = 1.98 ms, FA = 5°/6°, TI = 940ms/2830 ms, bandwidth = 240 Hz, matrix size = 256x256, 224 axial slices, acceleration factor = 3, voxel size = (0.75x0.75x0.75) mm^3.

Data Processing

For the MP2RAGE images, the background noise was removed using an extension (extension: https://github.com/benoitberanger/mp2rage) of Statistical Parametric Mapping 12 (SPM12; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) under Matlab R2019 (MathWorks, Natick, Massachusetts) (O'Brien et al., 2014). Then the images were reoriented using the 'spm_auto_reorient' function (https://github.com/CyclotronResearchCentre/spm_auto_reorient) and corrected for intensity non-uniformity using the bias correction method implemented in the SPM12 "unified segmentation" tool (Ashburner & Friston, 2005). To ensure optimal co-registration, brain extraction was done using SynthStrip (Hoopes et al., 2022) in Freesurfer (http://surfer.nmr.mgh.harvard.edu/). The brain-extracted T1-images were used to create a T1-weighted group template using Advanced Normalization Tools (ANTs, http://stnava.github.io/ANTs/) prior to normalization to the Montreal Neurological Institute (MNI) space using ANTs (1mm^3 voxel; MNI 152 template). The hypothalamus of each participant was segmented within 1mm^3 MNI 152 template into 5 subparts - inferior anterior, superior anterior, inferior tubular, superior tubular, posterior [cf. **Figure 3-2**-A] using an automatic computational approach (Billot et al., 2020).

For the EPI images, auto reorientation was applied on the images first. Then, voxel-displacement maps were computed from the phase and magnitude images associated with B0 map acquisition (taken right after the task), using the SPM fieldmap toolbox. To correct for head motion and static and dynamic susceptibility-induced variance, the "Realign & Unwarp" of SPM12 was then applied to the EPI images. The realigned and distortion-corrected EPI images then underwent brain extraction using the SynthStrip and then the final images were smoothed with a Gaussian kernel characterized by a FWHM = 3mm. The first level analyses were performed in the native space to prevent any possible error that may be caused by co-registration.

Statistical analyses

The whole-brain univariate analyses consisted of a general linear model (GLM) computed with SPM12. For the executive task, task blocks and light blocks were modelled as block functions. For the emotional task, the auditory stimuli were modelled as stick functions. For both tasks, a high-pass filter with a 256 s cut-off was applied to remove low-frequency drifts. For both tasks, stick

or block functions were convolved with the canonical hemodynamic response function. Movement and physiological parameters (cardiac, and respiration), which were computed with the PhysIO Toolbox (Translational Neuromodeling Unit, ETH Zurich, Switzerland), were included as covariates of no interest (Kasper et al., 2017).

Two separate analyses were completed. In the main analyses, we sought to test whether brain responses during the tasks were modulated by overall changes in illuminance level. The regressors of task blocks or events were accompanied by a single parametric modulation regressor corresponding to the light melanopic illuminance level (.16, 37, 92, 190 mel EDI). The contrasts of interest consisted of the main effects of the parametric modulation. In the subsequent post hoc analysis, we estimated the responses to the stimuli under each light condition. Separate regressors modelled each task's block or event type under each light condition (0, 0.16, 37, 92, 190 mel EDI). The contrasts of interest consisted of the main effects of each regressor.

The output masks of the segmentation procedure we used to extract regression betas associated with each of the hypothalamus subparts using the REX Toolbox (https://web.mit.edu/swg/software.htm) (Duff et al., 2007). Betas were averaged (mean) within each subpart and then across the homologous subparts of each hemisphere. In the main analyses this yielded 1 activity estimate per stimulus type and per hypothalamus subpart (i.e. 10 per individual), while in the subsequent analyses, we obtained 5 activity estimates per stimulus type and per subpart (50 per individual).

For visualization of whole-brain results over the entire sample, all statistical maps obtained from the first level analysis were first transferred to the group template space and then the MNI space ($1x1x1mm^3$ image resolution). All the registration steps were performed with ANTs. The visualisation was focused on the hypothalamus regions to assess whether increasing illuminance resulted in a local increase and/ or decrease of beta estimates within the hypothalamus or whether beta estimates were mainly influenced by a relatively unspecific and widespread increase in BOLD signal surrounding the hypothalamus.

Statistical analyses of the activity of the hypothalamus subparts were performed in SAS 9.4 (SAS Institute, NC, USA). Analyses consisted of Generalised Linear Mixed Models (GLMM) with the subject as a random factor (intercept and slope) and were adjusted for the dependent variable distribution. As the main statistical analysis was completed for each task, the significance threshold was corrected for multiple comparisons and was set at $p < 0.025$. Direct post hoc of the main analyses were corrected for multiple comparisons using a Tukey adjustment. The subsequent more detailed analyses were considered as post hoc that were not corrected for multiple comparisons ($p < 0.05$). To detect outlier values within the data sets, Cook's distance > 1 was used for exclusion. No outliers were detected for activity estimates of both tasks, while four outlier values were removed from the analyses of the 2-back and 0-back performance.

The main analyses included the activity estimates modulated by light illuminance as a dependent variable and the hypothalamus subpart and stimulus type (2-back/0-back - neutral/emotional) as repeated measures (autoregressive (1) correlation), together with age, sex and BMI as covariates. The second set of post hoc GLMM analyses included the activity estimates of the hypothalamus subparts as the dependent variable and hypothalamus subpart, stimulus type and

illuminance (0, 0.16, 37, 92, 190 mel EDI lux) as the repeated measures (autoregressive (1) correlation), together with age, sex, and BMI as covariates and interaction term between illuminance and hypothalamus subpart. The final set of analyses included performance metrics as dependent variables (accuracy to the 2-back or 0-back task - as percentage of correct responses; reaction time – ms - to emotional or neutral stimuli during the emotional task) and included the same repeated measures and covariates ads in the preceding set as well as activity of the relevant hypothalamus subpart.

Optimal sensitivity and power analyses in GLMMs remain under investigation (e.g. (Kain et al., 2015)). We nevertheless computed a prior sensitivity analysis to get an indication of the minimum detectable effect size in our main analyses given our sample size. According to G*Power 3 (version 3.1.9.4) (Erdfelder et al., 2009), taking into account a power of 0.8, an error rate α of 0.025 (correcting for 2 tasks), and a sample of 26 allowed us to detect large effect sizes $r > 0.54$ (two-sided; absolute values; CI: 0.19–0.77; $R^2 > 0.29$, R^2 CI: 0.04–0.59) within a multiple linear regression framework including one tested predictor (illuminance effect) and three covariates (age, sex and BMI).

Results

Twenty-six healthy young adults (16 women; 24.3 ± 2.9 y; **Appendix 2. Suppl Table 6-1**) completed two auditory cognitive tasks encompassing, respectively, the executive (Collette et al., 2005) and emotional (Grandjean et al., 2005) domains, while alternatively maintained in darkness or exposed to short periods (< 1 min) of light of four different illuminances (0.16, 37, 92, 190 melanopic equivalent daylight illuminance - mel EDI- lux; **Appendix 2. Suppl Table 6-2**) [**Figure 3-1**]. The hypothalamus of each participant was segmented into 5 subparts – inferior-anterior, superior-anterior, inferior-tubular, superior-tubular, and posterior [**Figure 3-2**-A] – so we could consistently extract the regional effect of illuminance change on fMRI blood-oxygen-level-dependent (BOLD) signal over most of the hypothalamus volume.

The impact of illuminance variations on the activity of the hypothalamus is not uniform

The main analyses aimed at isolating differences in the overall impact of illuminance changes among the 5 hypothalamus subparts. For each subpart, we extracted an index of the illuminance impact as their average regression coefficients between their responses to the tasks and the illuminance levels. These analyses showed significant differences between the hypothalamus subparts for the executive (generalized linear mixed models (GLMM); main effect of the subparts; $p = 0.002$) and emotional (GLMM; main effect of the subparts; $p < 0.0001$) tasks, revealing that, during both tasks, the variations in illuminance affected the activity of the 5 hypothalamus subparts differently [**Figure 3-2**-B, C; **Table 3-1**]. For both tasks, there was no significant main effect for any of the covariates and post hoc analyses showed that the index of

the illuminance impact was consistently different in the posterior hypothalamus subpart compared to the other subparts [pcorrected ≤ 0.05, except for the difference with superior tubular hypothalamus subpart during the emotional task: p-corrected = 0.09; **Table 3-1**]. Importantly, whole-brain analyses confirmed that increasing illuminance resulted in a local increase and decrease of activity that could be detected, respectively, over the posterior and inferior subparts of the hypothalamus [**Figure 3-2-**D-G]. This shows that our results do not come from a relatively unspecific and widespread increase in BOLD signal surrounding the hypothalamus subparts and that the effect of light was most prominent over the posterior and inferior-anterior subparts.

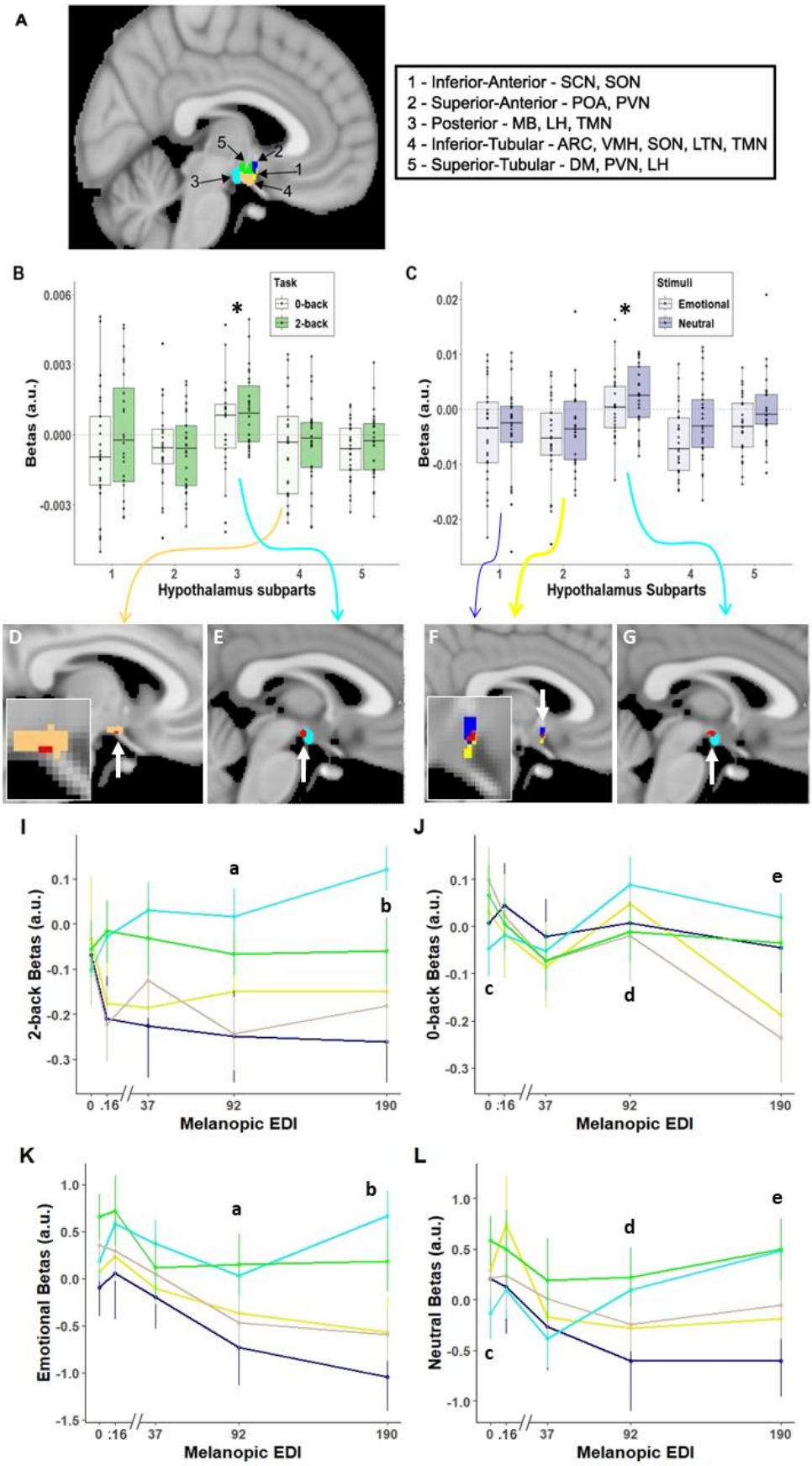

A
1 - Inferior-Anterior - SCN, SON
2 - Superior-Anterior - POA, PVN
3 - Posterior - MB, LH, TMN
4 - Inferior-Tubular - ARC, VMH, SON, LTN, TMN
5 - Superior-Tubular - DM, PVN, LH
B
Task
0-back
2-back
Betas (a.u.)
Hypothalamus subparts
C
Stimuli
Emotional
Neutral
Betas (a.u.)
Hypothalamus Subparts
D
E
F
G
I
2-back Betas (a.u.)
Melanopic EDI
J
0-back Betas (a.u.)
Melanopic EDI
K
Emotional Betas (a.u.)
Melanopic EDI
L
Neutral Betas (a.u.)
Melanopic EDI

Figure 3-2. Illuminance impact on the hypothalamus subparts.

(A) Segmentation of the hypothalamus in five subparts in a representative participant.

The nuclei encompassed by the different subparts are indicated in the right inset – according to (Billot et al., 2020). ARC: arcuate nucleus; DMH; dorsomedial nucleus; LH lateral hypothalamus; LTN: lateral tubular nucleus; MB: mamillary body; POA: preoptic area; PVN: paraventricular nucleus; PNH: posterior nucleus of the hypothalamus; SCN: suprachiasmatic nucleus; SON: supraoptic nucleus; TMN: tuberomammillary nucleus; VMN: ventromedial nucleus.

(B-C) Estimates (beta; arbitrary unit – a.u.) of the collective impact of illuminance variation on the activity of each hypothalamus subpart. (Refer to **Table 3-1** full statistics)

(B) Executive task: significant main effect of hypothalamus subparts (p=0.002), no significant main effect of task type (p=0.4) or subpart-by-task-type interaction (p=0.61). **(C)** Emotional task: significant main effect of hypothalamus subparts (p<.0001), no significant main effect of stimulus type (p=0.053) or subpart-by-stimulus-type interaction (p=0.7).

(D-G) Whole brain analyses of the collective impact of the variations in illuminance over the hypothalamus area **-** for illustration.

A local positive peak (red; $p_{uncorrected}$<0.001) was detected over the posterior hypothalamus subpart (light blue) in executive **(E)** and emotional **(G)**.

A local negative peak (red; $p_{uncorrected}$<0.001) was detected over the inferior-tubular hypothalamus subparts (light orange) during the executive task **(D)**, while local negative peak (red; $p_{uncorrected}$<0.001) was detected over the inferior-anterior (yellow) and superior-anterior §blue) hypothalamus subparts during the emotional task **(F)** – insets correspond to enlargements over the hypothalamus area.

Arrows from panels B and C arise from and are colour coded according to the hypothalamus subpart that is displayed in panels D to G.

These results indicate that our finding does not arise from a nearby "leaking“ activation/deactivation.

(I-L) Estimates of the impact of each illuminance on the activity of the hypothalamus subparts. (Refer for **Table 3-2** and **Appendix 2. Suppl Tables 6-3/4/5/6** for full statistics)

Activity dynamics across illuminance for each subpart (colour code as in A). Results are displayed per task or stimulus type although no interactions with task or stimulus type were detected. Significant illuminance-by-hypothalamus-subpart interactions were detected for **(I-J)** the executive task (p=0.041) and **(K-L)** the emotional task (p=0.041).

Small letter indicate significant difference ($p < 0.05$) between the following subparts at illuminance: **a.** 92 mel EDI lux: posterior vs. superior-anterior; posterior vs. inferior-tubular; **b.** 190 mel EDI lux: posterior vs. superior-anterior; posterior vs. inferior-tubular; **c.** 0 mel EDI lux: posterior vs. superior-tubular; **d.** 92 mel EDI lux: posterior vs. superior-anterior; superior-anterior vs. inferior-tubular; **e.** 190 mel EDI lux: posterior vs. inferior-anterior; posterior vs. superior-anterior; posterior vs. inferior-tubular; superior-anterior vs. superior-tubular; inferior-tubular vs. superior-tubular.

Opposite dynamics between the posterior and inferior/anterior hypothalamus at higher illuminance

This prompted us to assess the activity of the hypothalamus subparts under each illuminance to detail the different regional activity dynamics across the hypothalamus. The statistical analyses confirmed that the activity dynamics across illuminance levels differed between the 5 subparts during the executive and the emotional tasks (GLMM; subparts-by-illuminance interaction; $p = 0.041$) tasks [**Figure 3-2**-I-L; **Table 3-2**]. Post hoc contrasts first considered the impact of the changes in illuminance within each subpart (**Appendix 2. Suppl Tables 6-3/4**). The activity of the posterior hypothalamus subpart significantly ($p < 0.05$) increased under the highest illuminance (190 mel EDI) compared with darkness for both tasks and with the lower illuminances (37 and 92 mel EDI lux) for the emotional task. In contrast, for both tasks, the activity in the inferior-anterior and inferior-tubular hypothalamus subparts significantly ($p < 0.05$) decreased under the highest illuminance compared with darkness, and with lower illuminances for the emotional task. Finally, the activity of the superior anterior hypothalamus subpart decreased under higher illuminance during the emotional but not the executive task, while the activity of the fifth hypothalamus subpart, the superior tubular subpart, was not significantly affected by illuminance changes in either task.

Post hoc analyses also yielded several significant differences between hypothalamus subparts ($p < 0.05$) (**Table 3-2**; **Appendix 2. Suppl Tables 6-5/6**). For both tasks, the activity of the posterior hypothalamus subpart was consistently significantly higher than the activity inferior-tubular subpart under the highest illuminances (92 and 190 mel EDI lux). For the executive task, the activity of the posterior hypothalamus subpart was also significantly higher than the superior-anterior subpart under the highest illuminances (92 and 190 mel EDI lux). For the emotional task, the activity of the posterior hypothalamus subpart was also significantly higher than the superior-anterior subpart under the highest illuminances (190 mel EDI lux), while the activity superior-tubular hypothalamus subpart was significantly higher than the activity of the inferior-tubular, inferior-anterior and superior-anterior hypothalamus subparts (92 and/or190 mel EDI lux). The overall picture arising from these comparisons is that higher illuminance increased the activity of the posterior and superior hypothalamus subparts while it decreased the activity of the inferior and anterior hypothalamus subparts.

Performance to the executive task is improved by light and related to the activity of the posterior hypothalamus

Following these analyses, we explored whether the changes in activity across illuminances were related to cognitive performance. We first considered the more difficult (2-back) subtask of the executive task as it requires higher cognitive functions (see method for a full rationale) (Collette et al., 2005). The analysis revealed that accuracy to the executive task was high in all participants, but accuracy to the more difficult subtask (2-back) improved with increasing illuminance (GLMM; main effect of illuminance; $F = 2.72$; $p = 0.034$; Partial R2 215 = 0.1; **Figure 3-3**-A), controlling for

age, sex and BMI. Critically, the analysis also showed that performance under each illuminance was significantly related to the activity of the posterior hypothalamus subpart (GLMM; main effect of posterior subpart activity; $F = 9.43$; $p = 0.0027$; Partial R2 219 = 0.09). Surprisingly, the association was negative (**Figure 3-3**-B), suggesting that the part of variance explained by the hypothalamus subpart is distinct from the impact of light on performance. In contrast, no significant association was found when considering the activity of the other four subparts (GLMM; main effect of posterior subpart activity; $F < 0.62$; $p > 0.4$; **Figure 3-3**-C,D; **Appendix 2. Suppl Table 6-7**). We went on and found that the accuracy to the simpler control subtask of the executive tasks (0-back, see method) was not associated with the activity of the posterior hypothalamus subpart (GLMM controlling for age, sex and BMI; main effect of subpart activity; $F = 0.57$; $p = 0.45$; **Figure 3-3**-E), suggesting that the association with performance is specific to the 2-back subtask.

In the last step, we explored the reaction times during the emotional task (accuracy to the lure task is not meaningful). We found that reaction times to the emotional stimuli were not significantly affected by illuminance (GLMM controlling for age, sex and BMI; main effect of illuminance; $F = 1.01$; $p = 0.41$; **Figure 3-3**-F) and yet, they were significantly associated with the activity of the posterior hypothalamus subpart across each illuminance (GLMM; main effect of subpart activity; $F = 4.34$; $p = 0.04$; **Figure 3-3**-G). The association was positive meaning that reaction times were longer if activity estimates were higher, which could indicate a reinforcement of the emotional response characterized by longer reactions (Grandjean et al., 2005). No such significant association was detected when considering reaction times to the neutral items of the task (GLMM controlling for age, sex and BMI; main effect of illuminance; $F = 1.5$; $p = 0.21$; main effect of subpart activity; $F = 0.28$; $p = 0.6$; **Figure 3-3**-H).

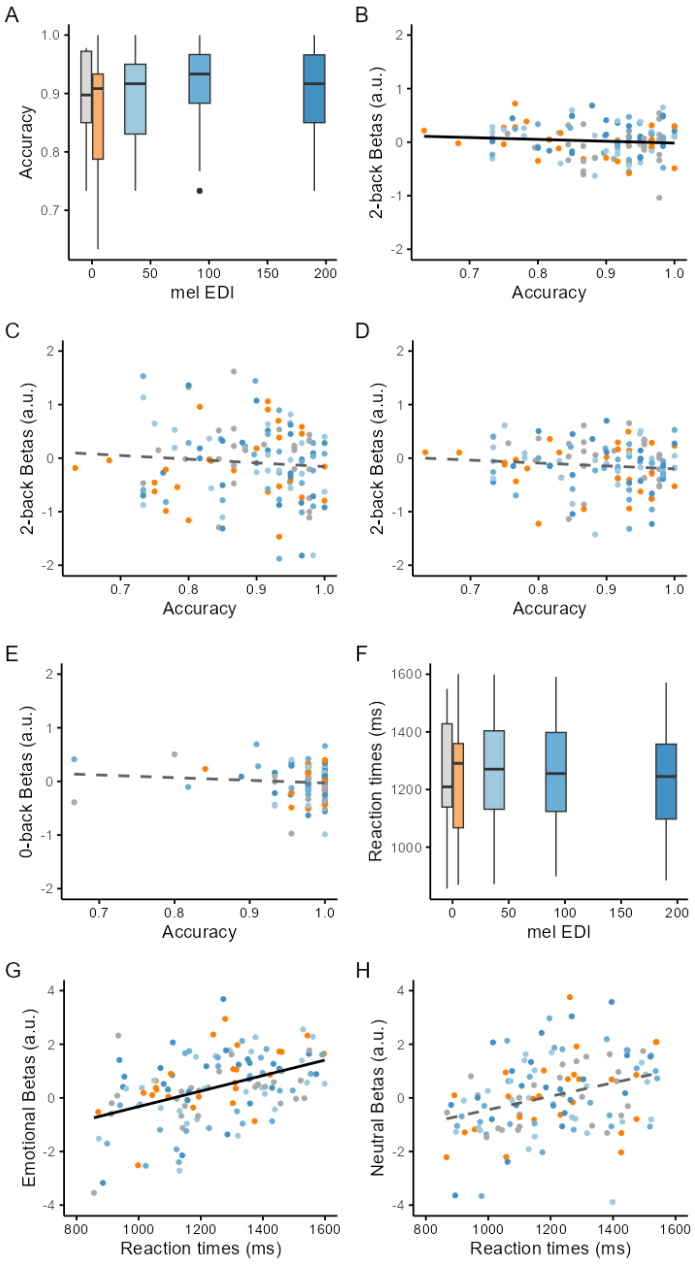


Figure 3-3. Impact of illuminance on performance and relationships with the activity of the posterior hypothalamus subpart. (A) Accuracy (percentage of correct responses) to the 2-back increased with increasing illuminance (p = 0.034). **(B)** Accuracy to the 2-back task is negatively correlated to the activity of the posterior hypothalamus subpart (p = 0.0027). **(C-D)** Accuracy to the 2-back task is not correlated to the activity of the inferior-anterior **(C)** and inferior-tubular **(D)** hypothalamus subparts (p > 0.4). Association between superior-anterior and superior-tubular subparts are not displayed but were not significant (p > 0.6). See Appendix 2. Suppl Table 6-7 for full details. **(E)** Accuracy to the 0-back task is not correlated to the activity of the posterior hypothalamus subpart (p = 0.45). **(F)** Reaction times to the emotional stimuli did not significantly change with increasing illuminance (p = 0.41). **(G)** Reaction times to the emotional stimuli are correlated to the activity of the posterior hypothalamus subpart (p = 0.04) with higher activity associated to slower reaction times. **(H)** Reaction times to the neutral stimuli are not correlated to the activity of the posterior hypothalamus subpart (p = 0.6). Solid and dashed lines correspond to the significant and not significant linear regression lines, respectively.

Tables

Table 3-1. Differences between hypothalamus subparts in the collective impact of the variation in illuminance on their activity.

Executive task							
Main GLMM				**Pairwise comparisons**			
Effect	**F value (df)**	**P value***	**Partial R^2**	**Contrast#**	**t-value**	**$P_{uncorrected}$**	**$P_{corrected}$**
Hypothalamus subparts	4.36 (4,225)	**0.002**	**0.08**	1 vs. 2	-0.30	0.76	0.99
				1 vs. 3	-3.48	**0.0006**	**0.0056**
				1 vs. 4	< 0.01	0.99	1
Task	0.74 (1,225)	0.4		1 vs. 5	-0.57	0.57	0.98
Hypothalamus subparts x task type	0.68 (4,225)	0.61		2 vs. 3	-3.17	**0.0017**	**0.015**
				2 vs. 4	0.31	0.76	0.99
				2 vs. 5	-0.27	0.79	0.99
Age	0.33 (1,22)	0.57		3 vs. 4	3.48	**0.0006**	**0.0055**
BMI	0.59 (1,22)	0.45		3 vs. 5	2.54	**0.0041**	**0.033**
Sex	0.01 (1,22)	0.91		4 vs. 5	-0.5	0.57	0.98
Emotional task							
Main GLMM				**Pairwise comparisons**			
Effect	**F Value**	**P value***	**Partial R^2**	**Contrast#**	**t-value**	**$P_{uncorrected}$**	**$P_{corrected}$**
Hypothalamus subparts	9.38 (4,194)	**<.0001**	**0.22**	1 vs. 2	0.32	0.75	0.99
				1 vs. 3	-4.76	**< 0.0001**	**< 0.0001**
				1 vs. 4	-0.05	0.96	1
Task	4.13 (1,25)	0.053		1 vs. 5	-2.24	**0.025**	0.17
Hypothalamus subparts x stimulus type	0.55 (4,194)	0.7		2 vs. 3	-5.09	**< 0.0001**	**0.0001**
				2 vs. 4	-0.37	0.71	0.99
				2 vs. 5	-2.57	**0.011**	0.081
Age	0.18 (1,22)	0.67		3 vs. 4	4.71	**< 0.0001**	**< 0.0001**
BMI	0.05 (1,22)	0.82		3 vs. 5	2.52	**0.013**	0.091
Sex	1.54 (1,22)	0.23		4 vs. 5	-2.19	**0.03**	0.19

Outputs of the generalized linear mixed model (GLMM) with subject as the random factor (intercept and slope), and task and subpart as repeated measures (ar(1) autocorrelation).

* The corrected p-value for multiple comparisons over 2 tests is $p < 0.025$.

Refer to Figure 3-1A for correspondence of subpart numbers

Table 3-2. Statistical outputs of GLMM testing for differences between the activity of each subpart of the hypothalamus under each illuminance

Executive task							
Main GLMM				**Comparisons between subparts per illuminance #**			
Effect	**F-value (df)**	**P value**	**Partial R^2**	**Illuminance***	**contrast**	**t-value**	**p-value**
Subpart	1.4 (4,228)	0.23		92	2 vs. 3	-2.25	**0.025**
Illuminance	2.15 (4,1017)	0.073		92	3 vs. 4	2.58	**0.01**
				190	1 vs. 3	-2.80	**0.0053**
Task	3.24 (1,228)	0.073		190	2 vs. 3	-2.24	**0.025**
Subpart x Illuminance	1.7 (16,1017)	**0.041**	**0.09**	190	3 vs. 4	3.15	**0.0017**
Age	1.19 (1,22)	0.29					
BMI	0.01 (1,22)	0.9					
Sex	0.38 (1,22)	0.54					

Emotional task							
Main GLMM				**Comparisons between subparts per illuminance #**			
Effect	**F-value (df)**	**P value**	**Partial R^2**	**Illuminance***	**contrast**	**t-value**	**p-value**
Subpart	4.29 (4,229)	**0.0023**	**0.07**	0	3 vs. 5	-2.05	**0.04**
				92	2 vs. 3	-2.53	**0.012**
Illuminance	9.41 (4,1020)	**< 0.0001**	**0.035**	92	2 vs. 5	-2.96	**0.0032**
				190	1 vs. 3	-3.31	**0.001**
				190	2 vs. 3	-4.75	**< 0.0001**
Task	0.13 (1,229)	0.72		190	1 vs. 5	-2.5	**0.013**
				190	2 vs. 5	-4.04	**<0.0001**
				190	3 vs. 4	3.13	**0.0018**
Subpart x Illuminance	1.7 (16,1020)	**0.041**	**0.026**	190	4 vs. 5	-2.32	**0.021**
Age	0.59 (1,22)	0.45					
BMI	1.54 (1,22)	0.23					
Sex	0.05 (1,22)	0.83					

* illuminance in mel EDI lux

Only significant comparisons are reported in the main text. For the full table, including post hocs comparing light levels within a subpart, refer to **Appendix 2. Suppl. Table 6-3/4/5/6/7**

Discussion

Animal research has established that the biological impact of light illuminance impinges on many subcortical structures, many of which regulate sleep and wakefulness (Campbell, Sharifpour, & Vandewalle, 2023; Hattar et al., 2006; Scammell et al., 2017; Tri & Do, 2019). How these findings translate to human beings is not established. Here, we took advantage of the relatively high resolution and signal-to-noise ratio of UHF 7T fMRI to determine how illuminance affects the activity of the hypothalamus as, based on animal research, it receives the densest projections from ipRGCs (Hattar et al., 2006; Tri & Do, 2019). We find that the activity of the posterior part of the hypothalamus increases with increasing illuminance while, in contrast, the inferior and anterior hypothalamus show a seemingly opposite pattern and see their activity decrease under higher illuminance. Importantly, performance to the complex cognitive task was improved under higher illuminance and was correlated to the activity of the posterior part of the hypothalamus under the different illuminance, though negatively. The results demonstrate that the human hypothalamus does not respond uniformly to variations in illuminance while engaged in a cognitive challenge and suggest that the posterior part of the hypothalamus may be key in mediating the stimulating impact of light on cognition.

The different nuclei of the hypothalamus do not have clear contrast boundaries based on MRI signals (Billot et al., 2020). As a result, achieving nucleus resolution over the human hypothalamus even using UFH MRI remains out of reach (Sharifpour et al., 2022). Therefore, we cannot assign the effects we report to a specific nucleus. We can only speculate and present a selection of plausible scenarios that would need to be tested. The posterior part of the hypothalamus - delineated in each participant based on an automatic reproducible procedure (Billot et al., 2020) - encompasses the MB as well as parts of the LH and the TMN. All these nuclei could participate to the increased BOLD signal we detect under higher illuminance. The LH and TMN, respectively, produce orexin and histamine, which are both known to promote wakefulness, while animal histology reports direct projection of the ipRGCs to the LH (Hattar et al., 2006; Scammell et al., 2017; Tri & Do, 2019). Orexin is a good candidate to constitute the circadian signal that promotes wakefulness and to counter the progressive increase in sleep needs with prolonged wakefulness (Zeitzer, 2013). Our data may therefore be compatible with an increase in orexin release by the LH with increasing illuminance. If this initial effect of light was maintained over a longer period of exposure, this would stimulate cognition and maintain or increase alertness (Campbell, Sharifpour, & Vandewalle, 2023) and may also be part of the mechanisms through which daytime light increases the amplitude in circadian variations of several physiological features (Bano-Otalora et al., 2021; Dijk et al., 2012). It could then also be part of the mechanisms through which evening light may disturb subsequent sleep (Chellappa et al., 2013) when illuminance is higher than the recommended maximum of 10 mel EDI lux for evening light (Brown et al., 2022). If the TMN was the hypothalamus nucleus underlying the regional increase in the BOLD signal we report, it could confer a role to histamine in mediating the stimulating impact of light. Of interest, the TMN receives orexin signal from the LH (Scammell et al., 2019). Alternatively, our findings may suggest a role for the MBs in mediating the impact of light on ongoing cognition, potentially influenced through its innervation by the TMN (Vann, 2010).

Previous research indicated that increasing illuminance reduced the activity of the anterior part of the hypothalamus encompassing the SCN, either following the exposure to light (Perrin et al., 2004) or during the exposure (Schoonderwoerd et al., 2022). We extend this finding by showing that the significant decrease in activity extends beyond the inferior anterior hypothalamus and therefore much beyond the SCN. The inferior-tubular and inferior-anterior subparts of the hypothalamus – also isolated based on an automatic reproducible procedure (Billot et al., 2020) - encompass several nuclei such as notably the SCN, SON, ventromedial nucleus of the hypothalamus, arcuate nucleus and part of the TMN. Again, all these nuclei may be involved in the reduction in BOLD signal we observe at higher illuminance. In terms of chemical communication, these changes in activity could correspond to a modification of the γ-aminobutyric acid (GABA) internal or external signalling of the SCN which has been implicated in its response to light (Albers et al., 2017). GABA produced by the SCN has also been reported to have excitatory properties such that the BOLD signal changes we report may correspond to a reduction in excitation (Albers et al., 2017). Likewise, the SCN is also producing other neuropeptides that could affect its downstream targets. As the inferior-tubular subpart of the hypothalamus also includes part of the TMN it may be the TMN and its GABA production that is decreased by higher illuminance (Scammell et al., 2019). The decrease in BOLD signal with increasing illuminance we report could therefore arguably reflect a decreased inhibitory signal arising from the anterior and inferior nuclei of the hypothalamus.

Importantly, none of the scenarios we elaborated on are mutually exclusive and we may have overlooked the potential implication of several nuclei as well as the cellular diversity of the nuclei of the hypothalamus (Adamantidis et al., 2019; Scammell et al., 2017). We further note that the anterior-superior hypothalamus subpart of the hypothalamus encompassing the VLPO and PON sees its activity decreasing under higher illuminance during the emotional task, similarly to the anterior-inferior and inferior-tubular areas. Likewise, similar to the posterior subpart, the activity of the superior-tubular hypothalamus subpart may be increased under higher illuminance during the emotional task. Whether this represents a task-specific effect arising, for instance, from differences in the salience of the auditory stimulus, remains to be determined.

A critical aspect of our results is that the performance to the 2-back (executive) subtask was significantly increased when exposed to higher illuminance light. The extent of this increase was limited, likely because performance was overall high at all illuminances, but was not detected for the simpler detection letter subtask (0-back). The result contrasts with many previous 3T MRI investigations on the biological effects of light on human brain function which did not report behavioural changes induced by repeated short exposures to light (e.g. (Vandewalle, Archer, et al., 2011; Vandewalle, Gais, et al., 2007; Vandewalle, Schmidt, et al., 2007) but see (Daneault et al., 2018; Vandewalle et al., 2006)). Our 7T MRI study, which includes a sample size larger than many of these previous studies, supports that BOLD fMRI is sensitive in detecting subtle impacts of light on the brain and that these detected changes can arguably contribute to the behavioural changes others reported using longer light exposure and other approaches (e.g. (Cajochen et al., 2011; Lockley et al., 2006) but see (Smolders et al., 2018)).

Importantly, we find that activity of the posterior hypothalamus subpart is negatively related to the performance to the executive task, making it unlikely that it mediates directly the positive impact of light on performance. The activity of the posterior hypothalamus was, however,

associated with an increased behavioural response to emotional stimuli. The association between behaviour and the posterior hypothalamus is therefore likely to be complex and may depend on the context, with for instance different nuclei or neuronal populations contributing in some instances but not in others (Adamantidis et al., 2019; Scammell et al., 2019). It is likely also to work jointly with the decreased activity of the anterior/inferior hypothalamus we detected as well as with other non-hypothalamus subcortical structures regulating wakefulness to influence behaviour, which intrinsically primarily depends on cortical activity. Future research should assess the impact of light on other subcortical structures and on the entire subcortical network to determine how illuminance modifies their crosstalk as well as their interaction with the cortex, to eventually lead to behavioural impacts. These analyses could for instance address whether the regional changes in activity of the hypothalamus we find are upstream of the repeatedly reported impact of light illuminance on the activity of the pulvinar in the thalamus (Campbell, Sharifpour, & Vandewalle, 2023; Vandewalle et al., 2006). Although it does not receive direct dense input from ipRGCs, it is likely to indirectly mediate the biological impact of light on ongoing cognitive activity (Paparella et al., 2023).

We based our rationale and part of our interpretations on ipRGC projections, which have been demonstrated in rodents to channel the NIF biological impact of light and incorporate the inputs from rods and cones with their intrinsic photosensitivity into a light signal that can impact the brain (Güler et al., 2008; Tri & Do, 2019). Given the polychromatic nature of the light we used, classical photoreceptors and their projections to visual brain areas may, however, have directly or indirectly contributed to the modulation by light of the regional activity of the hypothalamus.

All these knowledge gaps are important to address because acting on light stands as a promising means to reduce high sleepiness and improve cognitive deficits during wakefulness as well as to facilitate sleep in the few hours preceding bedtime (Brown et al., 2022; Didikoglu et al., 2023; Gooley et al., 2011; Munch et al., 2016; Riemersma-van der Lek et al., 2008; Scheuermaier et al., 2018; Wirz-Justice et al., 2020). Light therapy is also a validated means to improve mood and treat mood disorders (Glickman et al., 2006; Lam et al., 2016). Light administration can also be considered a simple means to disturb the brain circuitry regulating sleep and wakefulness such that it can provide insights about novel means to improve their quality. For instance, if orexin and histamine were part of the mechanism through which natural light affects brain functions, their administration may be the most ecological and/or natural means to affect alertness and cognition. Likewise, as both orexin and histamine are targets for the treatment of brain disorders, our findings could suggest that light may constitute a non-pharmacological complementary intervention to compounds that are being developed to treat arousal, sleep, or cognitive dysfunction in brain disorders (Ma et al., 2018). It remains, however, premature in our view to base recommendations on the therapeutic use of light based on the MRI findings gathered to date. Targeted lighting for interventions or for precise interference of subcortical circuits will require a full understanding of how light affects the brain, particularly at the subcortical level. Our findings represent an important step towards this goal, at the level of the hypothalamus.

Chapter 4

Exposure to light modulates the activity of the medial amygdala during emotional processing.

This chapter is based on our article under preparation:

Campbell, I., Balda Aizpurua, J. F., Sharifpour, R., Paparella, I., Beckers, E., Mortazavi, N., Berger, A., Koshmanova, E., Read, J., Zubkov, M., Talwar, P., Collette, F., Sherif, S., Philips, C., Lamalle, L., & Vandewalle, G. (2023). **Exposure to light modulates the activity of the human medial amygdala during emotional processing**. *Under preparation.*

Abstract

Light can influence several non-image-forming biological effects including modulation of mood and emotional processing. In humans, the neural circuitry underlying light's impact on emotional processing is not well established. A likely region of this circuit is the amygdala, as it is recognized as essential to emotional regulation, its activity is modulated by light and some nuclei receive retinal projections based on work in animal models. Here, we used 7 Tesla functional magnetic resonance imaging to assess the impact of variations in illuminance on the regional activity of the amygdala in healthy young adults (N = 29; 18 women; 24 ± 3.1y) during an auditory emotional task. We found several subregions of the amygdala, including the medial nucleus that receives direct projection from intrinsically photosensitive retinal ganglion cells, showed a marked and linear reduction of activity with increasing illuminance when processing emotionally charged stimuli. We speculate that it is through the medial nucleus that prolonged light exposure affects the emotional state of healthy individuals. These findings provide additional insight into the mechanisms that underlie the biological impact of light on the brain potentially improving our understanding of how light therapy could be beneficial in the treatment of mood disorders.

Introduction

The use of bright light therapy as a non-pharmacological treatment for seasonal affective disorder (SAD) has long been established and is also considered an adjunctive therapy for other non-seasonal psychiatric disorders (Penders et al., 2016; Pjrek et al., 2020). Previous research reported that the mechanisms of action of light on mood regulation in humans could involve: (i) the stimulation of serotonin and dopamine production, both of which show seasonality and have an essential role in mood (Praschak-Rieder & Willeit, 2012; Spindelegger et al., 2012; R. Zhang & Volkow, 2023); (ii) the normalisation of rod and cones functioning in the retina (Lavoie et al., 2009); (iii) the improvement of circadian entrainment (Lewy et al., 2006; R. Zhang & Volkow, 2023); (iv) or an impact on emotional processing (Vandewalle et al., 2010; Vandewalle, Hébert, et al., 2011). Although the exact mechanism of light's influence on mood in humans is still not fully established, it appears to be mediated through a light-sensitive pathway of the retina (Koorengevel et al., 2001; Legates et al., 2012) that detects environmental irradiance and is referred to as the non-image forming (NIF) or non-visual system (Campbell, Sharifpour, & Vandewalle, 2023). The NIF system mostly mediates light's influence on functions not directly related to image formation, including melatonin suppression (Brainard et al., 2001), stimulation of alertness and cognitive performance (Vandewalle et al., 2009) and on a longer timescale, light can affect circadian entrainment (Wirz-Justice et al., 2020). Intrinsically photosensitive retinal ganglion cells (ipRGCs) are the main photoreceptors of the NIF system. They express the photopigment melanopsin, which is maximally sensitive to blue-wavelength light (~480nm) and combines their intrinsic photosensitivity with inputs from rods and cones to influence multiple brain targets with a maximal efficiency shifted toward shorter blue-wavelength visible light (Güler et al., 2008; Lucas et al., 2014).

Interestingly, many of these targets are involved in mood regulation and emotional processing (Tri & Do, 2019). The perihabenular zone, ventral lateral geniculate nucleus and intergeniculate leaflet, all receive ipRGCs innervation and have been implicated in pathways mediating light's influence on depressive-like behaviours in animal models (An et al., 2020; L. Huang et al., 2019). Rodent data also showed that the amygdala, known to be important to mood regulation and emotional processing, is another region receiving direct inputs from ipRGCs (Šimić et al., 2021; Tri & Do, 2019). In rodents, ipRGCs project to the central nucleus of the amygdala and an ipRGC–central amygdala pathway was found to mediate anxiety-related behaviours through upregulation of corticosterone, after acute light exposure (Delwig et al., 2016; G. Wang et al., 2023). IpRCGs further project to the medial amygdala, a region known to be involved in anxiety-related behaviours (Davern & Head, 2011; Hattar et al., 2006; C. I. Li et al., 2004). Lesions of the medial amygdala in rodents induced altered light-enhanced startle and open-field behaviour, suggesting that the effects of light on anxiety may also be mediated by the ipRGCs innervation of the medial amygdala (Vinkers et al., 2010). In addition, chemogenetic activation of melanopsin-ipRGCs in rodents induced neural activity, in both the central and basolateral amygdala, as indicated by c-Fos expression (Milosavljevic et al., 2016).

Given the established involvement of the amygdala in psychiatric disorders in humans (Haris et al., 2023; Tse et al., 2023; Valizadeh et al., 2023), knowing exactly which of its nuclei respond to light may provide a reliable basis to extend the use of light treatment to a broader diversity of brain disorders.

An in vivo, task-based functional Magnetic Resonance Imaging (fMRI) study suggested enhanced responses to emotional stimuli in the amygdala as well as an increase in its crosstalk with the hypothalamus under blue-wavelength light in healthy humans (Vandewalle et al., 2010). In contrast, a resting-state fMRI study found that exposure to a warm polychromatic white light suppressed amygdala activity and its connectivity with the ventromedial prefrontal cortex during light exposure (McGlashan et al., 2021). The discrepancies may arise from the different characteristics of the light sources or from being engaged in a cognitive task vs. at being rest. Another explanation may arise from the context-dependent response of the different amygdala nuclei that could not be addressed given the available data resolution.

Here we aim to determine the impact of light exposure on the activity of the amygdala, and whether the dynamics varied across its volume, during the processing of emotional stimuli. We took advantage of the increased resolution of ultra-high-field (UHF) 7 Tesla (7T) fMRI to record the amygdala activity in healthy young adults exposed to varying illuminance while engaged in an auditory emotional task. We hypothesised that both the medial and central nuclei of the amygdala would show an increased activity with higher illuminance.

Methods

The data used in this paper originates from a large study that has led to several publications and part of the methods have been published previously (Beckers et al., 2023; Campbell, Beckers, et al., 2023; Campbell, Sharifpour, Aizpurua, et al., 2023; Paparella et al., 2023). The protocol was approved by the Ethics Committee of the Faculty of Medicine at the University of Liège. Participants gave their written informed consent to take part in the study and received monetary compensation for their participation.

Participants

Thirty-six healthy participants (23.9 y± 2.8; 23 women) gave their written informed consent to take part in the study. Exclusion criteria were assessed through questionnaires and a semi-structured interview: history of psychiatric and neurological disorders, sleep disorders, use of psychoactive drugs or addiction; history of ophthalmic disorders or auditory impairments; colour blindness; night shift work during the last year or recent trans-meridian travel during the last 2 months; excessive caffeine (>4 caffeine units/day) or alcohol consumption (>14 alcohol units/week); medication affecting the central nervous system; smoking; pregnancy or breast feeding (women). Their scores on the 21-item Beck Anxiety Inventory (Beck, Epstein, et al., 1988) and the Beck Depression Inventory-II (Beck et al., 1961) were minimal or mild (< 18) and minimal

(< 14), respectively. The chronotype was assessed with the Horne-Östberg questionnaire (Horne & Ostberg, 1976) and the seasonality with the Seasonal Pattern Assessment Questionnaire, (Rosenthal et al., 1984) but these metrics were not used for the inclusion of the participants.

For the analysis, 7 datasets were removed such that 29 participants (24 y± 3.1; 18 women; **Appendix 3. Supple Table 6-8**) were included in the analysis for the emotional task. Four participants failed the MRI quality control (QC) check, and the other three participants were excluded as they did not complete the entire emotional task.

Experimental Protocol

Structural images of the brain were acquired 1 to 2 weeks before the start of the experiment, during a visit which served as habituation to the experimental conditions. Participants then followed a loose sleep-wake schedule (±1h from habitual sleep/wake-up time) for 7 days, to maintain realistic entrained life conditions and avoid excessive sleep restrictions across all participants. Wrist actigraphy (AX3 accelerometer, Axivity, United Kingdom) and sleep diaries were used to verify sleep-wake schedules. Participants refrained from caffeinated and alcohol-containing beverages and excessive exercise for at least 3 days before the experiment. Data acquisitions took place in Liège, Belgium, between December 2020 and May 2023.

Participants arrived at the laboratory 1.5 to 2 hours after their habitual wake-up time for the experimental fMRI scans. To standardise participants' light history before the fMRI session, they were exposed to 5 minutes of bright white light (1000 lux) and were then maintained in dim light (<10 lux) for 45 minutes. During the dim light exposure, participants were given instructions about the fMRI cognitive tasks and completed practice tasks on a luminance-controlled laptop (< 10 lux). The fMRI session consisted of participants completing an executive task (25-min), an attentional task (15-min), and an emotional task (20-min) [**Figure 4-1**-A]. Participants always completed the executive task first as it was the most demanding task. The order of the following two tasks was counterbalanced across participants. Only the emotional task is discussed in the present paper. An eye-tracking system (EyeLink 1000Plus, SR Research, Ottawa, Canada) was monitored for proper eye-opening during all data acquisitions.

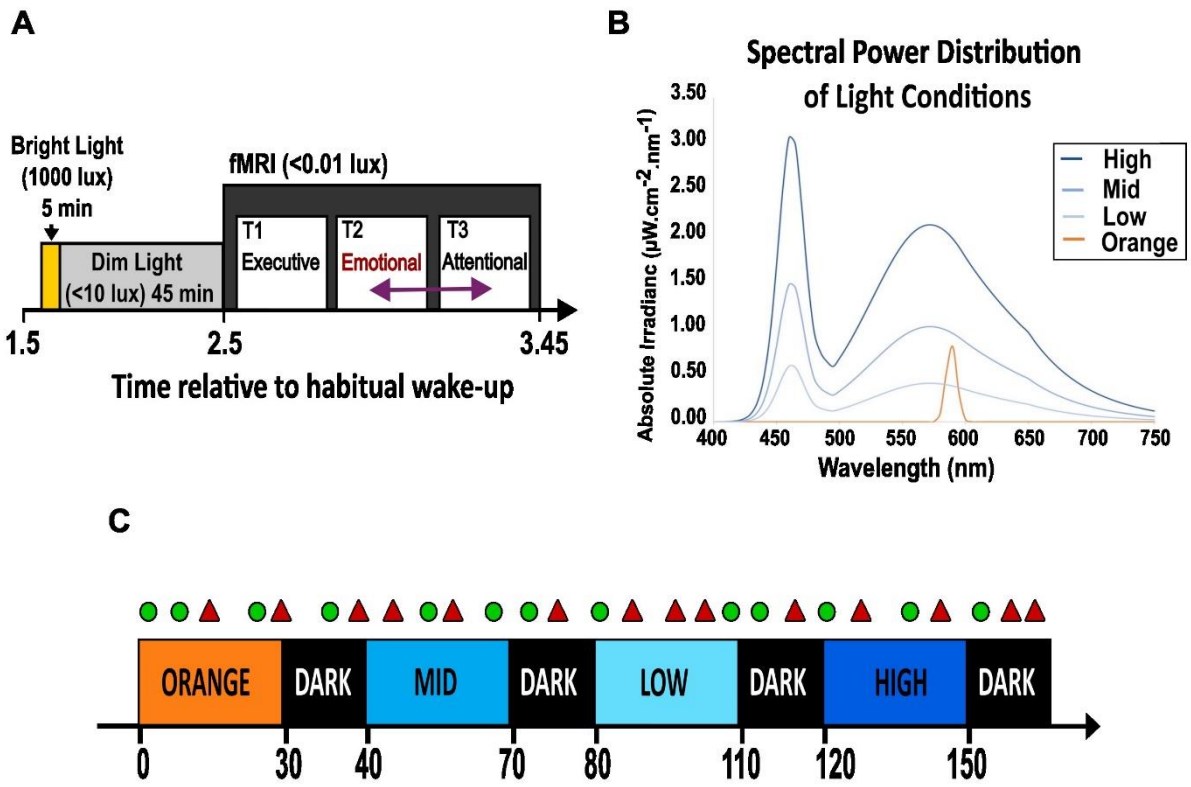


Figure 4-1. Experimental protocol

(A) Overall timeline. After prior light history standardisation, participants performed executive (always first), emotional and attentional tasks (pseudo-randomly 2nd or 3rd, violet arrow). Only the emotional task is considered in the present manuscript. **(B)** Spectral power distribution of light exposures. Monochromatic orange: 0.16 mel EDI lux; Polychromatic, blue-enriched light (6500K); LOW, MID, HIGH: 37, 92, 190 mel EDI lux. For the present analyses, we discarded colour differences between the light conditions and only considered illuminance as indexed by mel EDI lux. (See Appendix 3. Suppl Table 6-9 for full details). **(C)** Emotional task procedure. Time is reported in seconds relative to session onset; participants were pseudo-randomly exposed to the four light conditions. The emotional task consisted of a lure gender discrimination of vocalizations of three pseudo-word types ('goster', 'niuvenci', or 'figotleich') whilst exposed to the alternating white BEL of three different intensities (37, 92, 190 mel EDI lux; 6500 K) (LOW, MID, HIGH) and a monochromatic orange (0.16 mel EDI lux; 589mn) light. Light exposures lasted 30–40 s and were separated by 15–20-s periods of darkness. Untold to the participants, vocalisations were pronounced with angry (red triangles) and neutral (green circles) prosody pseudo-randomly and equally distributed across the light conditions.

Light Exposure

An MRI-compatible light system designed-in-lab was developed to ensure relatively uniform and indirect illumination of participants' eyes whilst in the MRI scanner. An 8-m long MRI-compatible dual-branched optical fibre (1-inch diameter, Setra Systems, MA, USA) transmitted light from a light box (SugarCUBE, Ushio America, CA, USA), that was stored in the MRI control room. The dual end of the optic fibre was attached to a light stand fitted at the back of the MRI coil, allowing for reproducible fixation and orientation of the optical fibre ends. The dual branches illuminated the inner walls of the head coil to illuminate indirectly the participants' eyes. A filter wheel (Spectral Products, AB300, NM, USA) and optical fibre filters to switch between a narrowband 589nm filter (full width at half maximum: 10 nm) and a UV long-bypass filter (433 – 1650nm) filter) and alternate between a monochromatic orange light and the full output of the polychromatic, blue-enriched LEDs (6500K) (**Figure 4-1**-B and **Appendix 3. Suppl Table 6-9** for in-detail light characteristics). Participants were asked to keep their eyes open and try not to blink too much during the cognitive tasks.

During the emotional task, participants were exposed to 30 to 40s periods of light blocks (median 35s) separated by 20s of darkness (<0.1 lux). The light conditions used were three different illuminances of a blue-enriched white LED light (37, 92, 190 melanopic equivalent daylight illuminance -mel EDI- lux) and the monochromatic orange light (0.16 mel EDI lux). The light blocks were repeated five times for each light condition.

The emotional task was programmed with Opensesame (3.2.8) (Mathôt et al., 2012) and launched from a computer in the MRI control room. Participants heard the auditory stimuli through MR-compatible headphones (Sensimetrics, Malden, MA) and the volume was set by the participant before starting the tasks to ensure a good auditory perception. Participants used an MRI-compatible keypad to respond to task items (Current Designs, Philadelphia, PA). The spectra of the lights were assessed at the end of the optical fibre (AvaSpec-2048, Avantes, The Netherlands). Illuminance could not be measured directly in the MRI bore, but the light source was calibrated prior to the experiment (840-C power meter, Newport, Irvine, CA).

Emotional Task

The emotional task used was a gender discrimination of auditory vocalizations task (Banse & Scherer, 1996). Participants were asked to use the keypad to indicate what they believed the gender of the person pronouncing each token was. The gender classification was a lure task ensuring participants paid attention to the auditory stimulation. The purpose of the task was to trigger an emotional response as participants were not told that 50% of the stimuli were pronounced with angry prosodies. The 240 auditory stimuli were pronounced by professional actors (50% women) and consisted of three meaningless words ("goster", "niuvenci", "figotleich"). The stimuli were expressed in either an angry or neutral prosody, which has been validated by behavioural assessments (Banse & Scherer, 1996) and in previous experiments (Grandjean et al., 2005; Sander et al., 2005). The stimuli were also matched for the duration (750

ms) and mean acoustic energy to avoid loudness effects. During each 30 to 40-s light block, four angry prosody stimuli and four neutral prosody stimuli were presented in a pseudorandom order and delivered every 3 to 5 s. A total of 160 distinct voice stimuli (50% angry; 50% neutral) were distributed across the four light conditions. The darkness period separating each light block contained two angry and two neutral stimuli. A total of 80 distinct voice stimuli (50% angry; 50% neutral) were distributed across the darkness periods. The instruction was to privilege accuracy over rapidity when responding.

Data acquisition

The MRI data were acquired in a 7T MAGNETOM Terra MR scanner (Siemens Healthineers, Erlangen, Germany) with a 32-channel receiver and 1-channel transmitter head coil (Nova Medical, Wilmington, MA, USA). Dielectric pads (Multiwave Imaging, Marseille, France) were placed between the subject's head and receiver coil to homogenize the magnetic field of the radio frequency (RF) pulses.

Multislice T2*-weighted fMRI images were obtained with a multi-band Gradient-Recalled Echo - Echo-Planar Imaging (GRE-EPI) sequence using axial slice orientation (TR = 2340 ms, TE = 24 ms, FA = 90°, no interslice gap, in-plane FoV = 224 mm × 224 mm, matrix size = 160 × 160 × 86, voxel size = 1.4 × 1.4 × 1.4 mm^3). To avoid the steady-state formation effects the first three scans were discarded. To correct for physiological noise in the fMRI data the participants' pulse and respiration movements were recorded using a pulse oximeter and a breathing belt (Siemens Healthineers, Erlangen, Germany). Following the fMRI acquisition a 2D GRE field mapping sequence with the following parameters: TR = 5.2 ms, TEs = 2.26 ms and 3.28 ms, FA = 15°, bandwidth = 737 Hz/pixel, matrix size = 96 × 128, 96 axial slices, voxel size = (2 x 2 x 2) mm^3, acquisition time = 1:38 min, was acquired to assess B0 magnetic field inhomogeneities.

For the anatomical image, a high-resolution T1-weighted image was acquired using a Magnetization-Prepared with 2 RApid Gradient Echoes (MP2RAGE) sequence: TR = 4300 ms, TE = 1.98 ms, FA = 5°/6°, TI = 940ms/2830 ms, bandwidth = 240 Hz, matrix size = 256x256, 224 axial slices, acceleration factor = 3, voxel size = (0.75 x 0.75 x 0.75) mm^3.

Data pre-processing

For the MP2RAGE images, the background noise was removed using an extension (https://github.com/benoitberanger/mp2rage) of Statistical Parametric Mapping 12 (SPM12; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) under Matlab R2019 (MathWorks, Natick, Massachusetts) (O'Brien et al., 2014). Then the images were automatically reoriented (i.e. setting the image origin close to the Anterior Commissure and the AC-PC line horizontal) using the 'spm_auto_reorient' function (https://github.com/CyclotronResearchCentre/spm_auto_reorient) and corrected for intensity non-uniformity using the bias correction method implemented in SPM12 "unified segmentation"

tool (Ashburner & Friston, 2005). To ensure optimal co-registration, brain extraction was done using SynthStrip (Hoopes et al., 2022) in Freesurfer (http://surfer.nmr.mgh.harvard.edu/). The brain-extracted T1-images were used to create a T1-weighted group template using Advanced Normalization Tools (ANTs, http://stnava.github.io/ANTs/) before normalization to the Montreal Neurological Institute (MNI) space using ANTs (1mm³ isotropic voxel; MNI 152 template).

For the EPI images, auto reorientation was applied on the images first. Then, voxel-displacement maps were computed from the phase and magnitude images associated with B0 map acquisition (taken right after the task), using SPM fieldmap toolbox. To correct for head motion and static and dynamic susceptibility-induced variance, "Realign & Unwarp" function of SPM12 was then applied to the EPI images (Hutton et al., 2002). The realigned and distortion-corrected EPI images underwent brain extraction using the SynthStrip and the final images were smoothed with a Gaussian kernel characterized by a full width at half maximum of 3mm.

For each subject, the first level analysis was performed in the native space to prevent any possible bias that may be caused by caused by elastic deformation. Before the second level analysis, all statistical maps obtained from the first level analysis were first transferred to the group template space and then the (Montreal Neurological Institute) MNI space (1x1x1mm^3 image resolution; MNI 152 template). All the registration steps were performed with ANTs.

Statistical analysis

Our analysis consisted of an a priori region of interest focusing on the activity of the amygdala which was estimated as part of a univariate analysis of the whole brain. This whole-brain analysis consisted of a general linear mixed model (GLMM) computed with SPM12. For the emotional task, the auditory stimuli were modelled as stick functions and a high-pass filter with a 256 s cut-off was applied to remove low-frequency drifts. Stick functions were convolved with a canonical hemodynamic response function. Movement and physiological parameters (cardiac, and respiration), the time-series for which were computed with the PhysIO Toolbox (Translational Neuromodeling Unit, ETH Zurich, Switzerland), were included as covariates of no interest (Kasper et al., 2017).

There were two parts to the whole-brain analysis. In the main analysis, we assessed how brain responses during the task were modulated by overall changes in illuminance level. The two regressors of task events (neutral, angry) were each accompanied by a single parametric modulation corresponding to the light melanopic illuminance level (0, 0.16, 37, 92, 190 mel EDI). The contrasts of interest consisted of the main effect of the parametric modulations. In the subsequent part of the whole-brain analysis, we assessed the responses to the stimuli under each light condition. Separate regressors modelled each task's event type under each light condition (0, 0.16, 37, 92, 190 mel EDI). The contrasts of interest consisted of the main effects of each regressor.

We used an amygdala atlas to segment the region into 10 subparts (bihemispheric) in the MNI standard space (Tyszka & Pauli, 2016), corresponding to nuclei or nucleus groups (see **Figure 4-2**-A for template regions). The REX Toolbox (https://web.mit.edu/swg/software.htm) was used

to extract the activity estimates (betas) associated with the stimuli and light conditions from each amygdala subpart in both whole-brain analyses (Duff et al., 2007). The first analysis yielded 1 activity estimate per stimulus type and per amygdala subpart and the second analysis obtained 5 activity estimates per stimulus and amygdala subpart.

Statistical analyses of the activity of the amygdala subparts were performed in SAS 9.4 (SAS Institute, NC, USA). Analyses consisted of fitting the GLMM with the subject as a random factor (intercept and slope) and were adjusted for the dependent variable distribution. As both parts of the statistical analysis (main analyses and post hoc GLMMs) included all subparts, light conditions and stimulus types, in a single model, the significance threshold was not corrected for multiple comparisons and was set at $p < 0.05$. Direct post hoc of the main analyses were corrected for multiple comparisons using a Tukey adjustment. Activity estimates were considered outliers if they were outside the $> \pm 3$ standard deviations (SDs) range across the emotional stimuli and the light level and were removed.

The main analyses included the activity estimates modulated by light illuminance as a dependent variable and the amygdala subparts and stimulus type (neutral/angry) as repeated measures (autoregressive (1) correlation), together with age, sex and BMI as covariates. The second set of post hoc GLMM analyses included the activity estimates of the amygdala subparts as the dependent variable and amygdala subpart, stimulus type and illuminance (0, 0.16, 37, 92, 190 mel EDI lux) as the repeated measures (autoregressive (1) correlation), together with age, sex, and BMI as covariates and an interaction term between illuminance and amygdala subpart. The final set of analyses included performance metrics as dependent variables (reaction time – milliseconds - to emotional or neutral stimuli during the emotional task) and included the same repeated measures and covariates as in the preceding set as well as activity of the relevant amygdala subpart.

Whole brain results over the entire sample were used for visualization purposes only, following normalization to MNI standard space. The visualisation focussed on the amygdala regions to assess whether increasing illuminance resulted in local increases or decreases of activity estimates. Visualisation was then confirmed to the local significant differences detected within the amygdala in the GLMM analyses to assess whether they were truly due to local changes in the BOLD signal or activity estimates were mainly influenced by a relatively unspecific widespread increase in BOLD signal surrounding the amygdala.

Optimal sensitivity and power analyses in GLMMs remain under investigation (e.g. (Kain et al., 2015)). We nevertheless computed a prior sensitivity analysis to get an indication of the minimum detectable effect size in our main analyses given our sample size. According to G*Power 3 (version 3.1.9.4), (Erdfelder et al., 2009) taking into account a power of 0.8, an error rate α of 0.05, and a sample of 29 allowed us to detect medium effect sizes $r > 0.47$ (two-sided; absolute values; CI: 0.12–0.71; $R^2 > 0.22$, R^2 CI: 0.02–0.5) within a linear multiple regression framework including two tested predictors (illuminance effect, amygdala subpart) and four covariates (stimulus type, age, sex and BMI).

Results

Twenty-nine healthy young adults (24 y± 3.1; 18 women; **Appendix 3. Suppl 6-8**) completed an emotional auditory cognitive task, while alternatively maintained in darkness or exposed to short periods (< 1 min) of light of four different illuminances (0.16, 37, 92, 190 mel EDI lux; **Appendix 3. Suppl 6-9**) [**Figure 4-1**-C]. The performance of the emotional task was high, with a mean (SD) of 92% (7.3%) of button responses to the stimuli. The accuracy of the lure gender classification task (Grandjean et al., 2005), which is not relevant to the experiment, was on average 79.7% (SD: 9.9%), which is slightly lower than reported in previous studies using the same task (Sander et al., 2005; Vandewalle et al., 2010). Critically, the reaction times were significantly faster for the neutral stimuli (mean (SD) of 1203 ±183 ms) as compared with the emotional stimuli (mean (SD) of 1249 ±184 ms) (GLMM; main effect of stimulus type; $F_{[1,9.99]} = 21.53$; p=0.0009). This is in line with the previously reported literature (Sander et al., 2005; Vandewalle et al., 2010) and confirms that the emotional content of the stimuli was successful in triggering a behavioural response [**Figure 4-2**-B]. The reaction times to the neutral or emotional stimuli were not significantly affected by illuminance (neutral stimuli, $F_{[4,42.32]} = 1.22$, p = 0.3; emotional stimuli, $F_{[4,39.69]} = 0.56$, p = 0.6). This does not, in principle, preclude light from affecting brain activity and it ensures that modifications in brain activity are not merely the results of a change in reaction times.

To test how light may affect the regional activity of the amygdala, we used a template that consistently divided the amygdala into 10 subparts (Tyszka & Pauli, 2016), corresponding to nuclei or nuclear groups (**Figure 4-2**-A) and allowed extraction of the effect of illuminance change on fMRI blood-oxygen-level-dependent (BOLD) in each of these subparts.

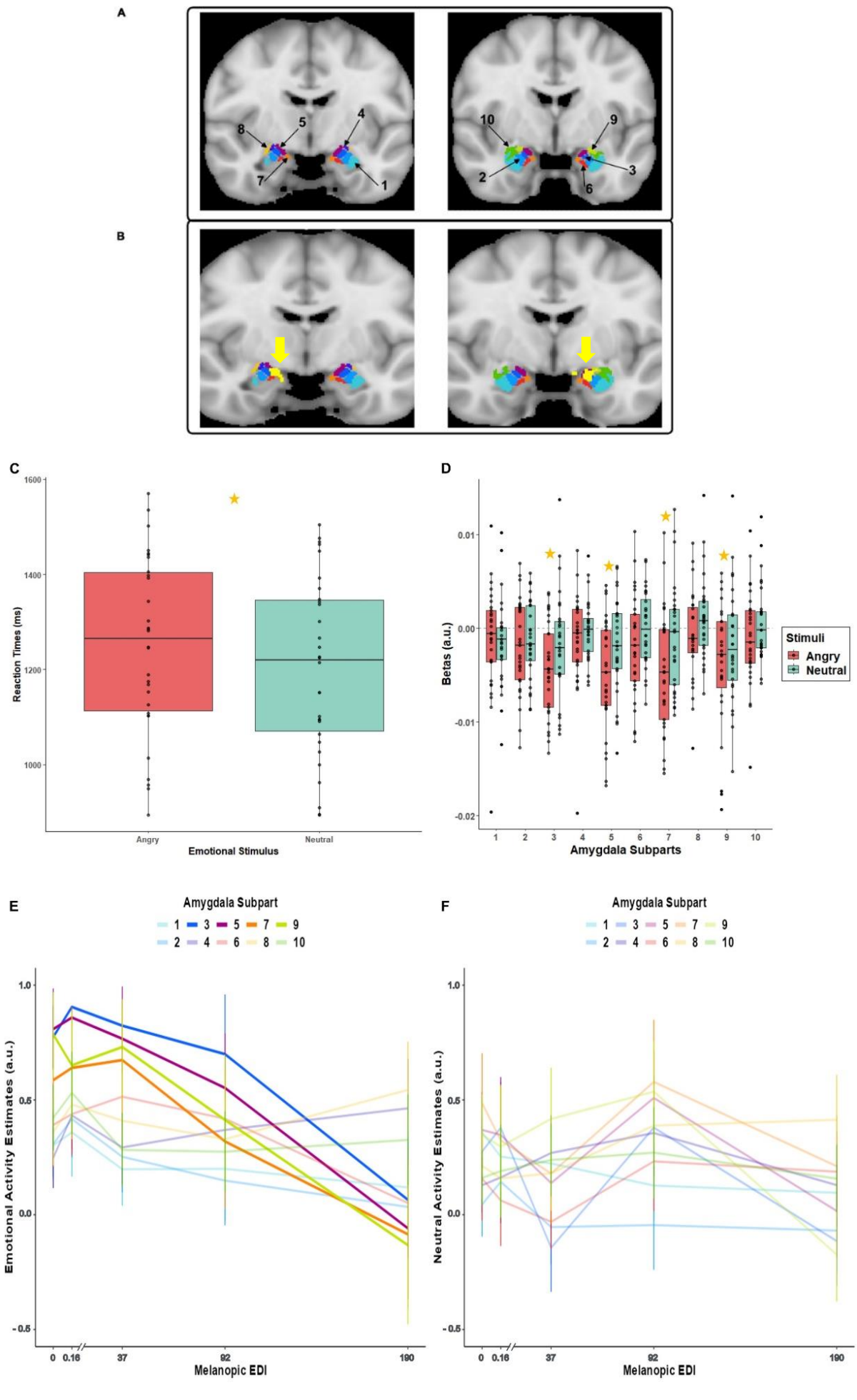

A
B
8
5
4
7
1
10
9
2
3
6
C
Reaction Times (ms)
1600
1400
1200
1000
Angry
Neutral
Emotional Stimulus
D
Betas (a.u.)
0.01
0.00
-0.01
-0.02
1 2 3 4 5 6 7 8 9 10
Amygdala Subparts
Stimuli
Angry
Neutral
E
Amygdala Subpart
1 3 5 7 9
2 4 6 8 10
Emotional Activity Estimates (a.u.)
1.0
0.5
0.0
- 0.5
0 0.16 37 92 190
Melanopic EDI
F
Amygdala Subpart
1 3 5 7 9
2 4 6 8 10
Neutral Activity Estimates (a.u.)
1.0
0.5
0.0
- 0.5
0 0.16 37 92 190
Melanopic EDI

Figure 4-2. Illuminance impact on the amygdala subparts.

(A) Segmentation of the amygdala into ten subparts. The amygdala template isolate nuclei and nucleus groups as follows: (1) Lateral nucleus, (2) Intermediate and dorsal basolateral nucleus, (3) Basomedial nuclei, (4) Central nucleus, (5) Medial and Cortical nuclei, (6) Ventral basolateral nucleus and Paralaminar nucleus, (7) amygdala transition area (ATA) composed of Amygdalocortical area, Amygdalohippocampal area, Periamygdaloid cortex, (8) Amygdalostriatal, (9) Anterior amygdaloid area (AAA), (10) Intercalated nuclei (Tyszka & Pauli, 2016).
(B) Visualization of the whole brain results over the entire sample. Whole brain analyses of the collective impact of the emotional variations in illuminance over the amygdala area. A local negative peak (yellow arrow and yellow cluster; puncorrected<0.001) was detected bilaterally in the amygdala mostly over the subparts 3, 5 and 7 in the left hemisphere and over subparts 3, 5 and 9 in the right hemisphere. These results indicate that our finding does not arise from a nearby "leaking“ deactivation.
(C) Reaction times to neutral (mean (SD) of 1203 (183) and angry (mean (SD) of 1203 (183) ms) stimuli ($p<0.001$) is shown.
(D) Estimates (beta; arbitrary unit – a.u.) of the collective impact of illuminance variation on the activity of each amygdala subpart. Significant main effect of amygdala subparts ($p <.0001$), significant main effect of stimulus type ($p <.0001$) and no subpart-by-stimulus-type interaction ($p = 0.4$) is depicted.
(E-F) Estimates of the impact of each illuminance on the activity of the amygdala subparts. Results are displayed per stimulus type. Significant amygdala subparts are highlighted in bold. Significant stimulus type-by-illuminance interaction ($p = 0.001$) and significant illuminance-by-amygdala interaction was detected ($p = 0.04$). (Refer to Table 3 & 4 and Suppl. Tables S3-S4 for full statistics).

Impact of illuminance variation on the activity of the amygdala

The first analysis isolated the differences in the overall impact of illuminance variation between the 10 amygdala subparts. An index of the illuminance impact was extracted for each subpart, as a reflection of the linear changes in their responses to the task stimuli as a function of illuminance levels. There were significant differences among the amygdala subparts (GLMM; main effect of the subparts; p <.0001), revealing that the variations in illuminance affected the activity of the 10 amygdala subparts differently [**Figure 4-2**-D, **Table 4-1**]. There was also a significant effect of emotional stimulus type (GLMM; main effect of the stimuli; p = <.0001) indicating that the illuminance impact varied with stimulus type. However, there was no interaction between the stimulus type and the amygdala subpart (GLMM; interaction; p = 0.4) and no significant main effect of covariates (sex, age, BMI). The post hoc analyses compared subparts and found that the basomedial nucleus (subpart 3 in dark blue in **Figure 4-2**-A), medial and cortical nuclei (subpart 5 in violet in **Figure 4-2**-A), amygdala transition areas (ATA) (subpart 7 in orange in **Figure 4-2**-A), and anterior amygdaloid area (AAA) subparts (subpart 9 in light green in **Figure 4-2**-A) are reacting significantly differently to light illuminance compared to some of the amygdala subparts [**Table 4-2**]. Interestingly, the medial and cortical subpart were significantly different from the central nucleus subpart. Overall, the results suggest that the medial and superior region of the amygdala - encompassing four subparts of our template – reacts differently to illuminance change than the rest of the amygdala and undergoes an overall decrease of activity with increasing illuminance.

Amygdala subparts under each illuminance

Following our main analysis, we then aimed to determine in more detail the regional impact of light across the amygdala as our main analyses may have missed for instance a non-linear relationship between activity in the amygdala and illuminance. We investigated the regional activity of each subpart under each illuminance. As in the main analysis, we confirmed that there was a significant impact of stimulus type (p = <.0001) and light level (p = <.0001) on the subpart activity, while there was no significant main effect of amygdala subparts (p = 0.1). Critically, on top of a significant interaction between illuminance and stimulus types (GLMM; task-by-illuminance; p = 0.001), the analyses further yielded an illuminance-by-subpart-interaction confirming that the impact of illuminance significantly varied across subparts (GLMM; subparts-by-illuminance interaction; p = 0.04) [**Figure 4-2**-E, F **Table 4-3**].

We computed post hoc contrasts and first considered the impact of the changes in illuminance within each amygdala subpart (**Table 4-4; Appendix 3. Suppl Table 6-10**). We found that the activity of the four medial/superior subparts isolated in the main analysis (basomedial nucleus -light blue-, medial and cortical nuclei -purple-, ATA -light green-, AAA -orange-) was significantly decreased under the highest illuminance (190 mel EDI lux) when compared to darkness (0 mel EDI lux) and the lowest illuminance level (0.16 mel EDI lux). The activity of three of the four nuclei- the basomedial nucleus, medial and cortical nuclei, and amygdala transition areas- were also significantly decreased when compared to blue-enriched light of the lower illuminances (37, 92 mel EDI lux). Importantly, there were no significant differences between the other amygdala

subparts. Next, the post-hoc tests examined differences between amygdala subparts under each illuminance (**Appendix 3. Suppl Table 6-11**) and found only the AAA subpart (orange) was significantly different from the amygdalostriatal transition area subpart (light orange) at the highest illuminance level (190 mel EDI lux). There was no significant difference between subparts at any other illuminance levels (for post hoc comparisons considering stimulus type and/or illuminance irrespective of amygdala subparts, see **Appendix 3. Suppl Tables 6-12, 13**).

Overall, these analyses confirm the results of the main analysis. They further indicate that increasing illuminance progressively and relatively linearly decreases the activity of the medial/superior regions of the amygdala specifically for the processing of emotional stimuli while activity was more stable across the rest of the amygdala irrespective of the illuminance changes and stimulus type.

Performance and amygdala activity

In the last step, we assessed whether the activity of one of these four subparts were related to performance in the emotional task. We found that the association between the activity of the AAA subpart and the reaction times to the emotional stimuli reach nominal significance (GLMM; main effect of subpart activity; $F_{[1,115]}$ =3.63; p = 0.05; **Figure 4-3**-A) while reaction times were not significantly affected by illuminance. The association was negative suggesting that the part of variance explained by the amygdala subpart is distinct from the impact of light on performance. No such significant association was detected when considering reaction times to the neutral items of the task (GLMM controlling for age, sex and BMI; main effect of illuminance; $F_{[4,104]}$ = 0.93; p = 0.4; main effect of subpart activity; F = 0.03; p = 0.8; **Figure 4-3**-B). No significant association was found when considering the activity of the other subparts.

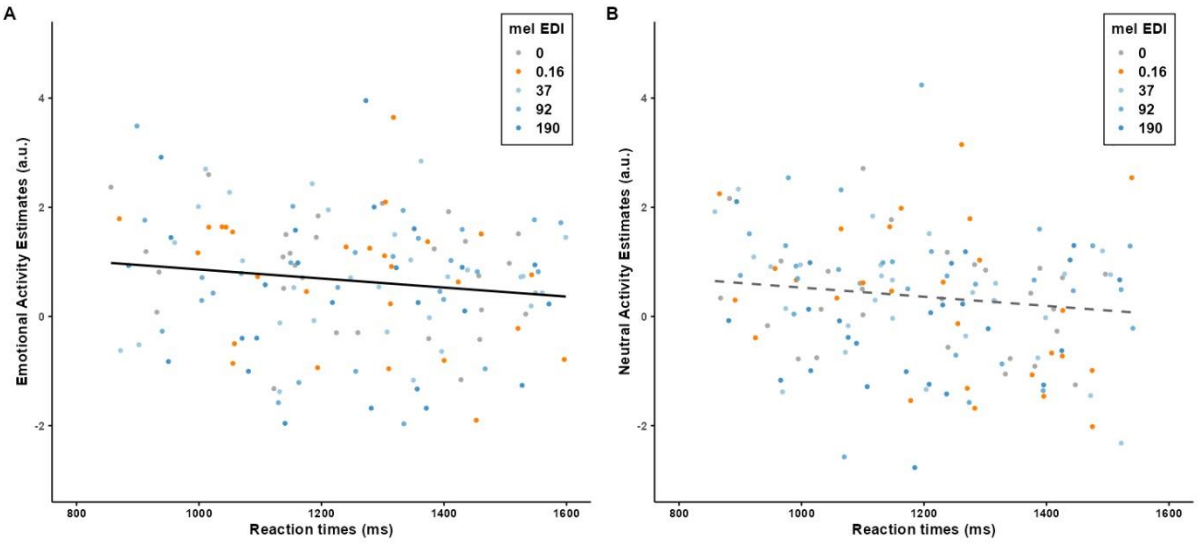


Figure 4-3. Impact of illuminance on performance and relationships with the activity of the anterior amygdaloid area subpart.

(A) Reaction times to the emotional stimuli are correlated to the activity of the anterior amygdaloid area subpart ($p = 0.05$). **(B)** Reaction times to the neutral stimuli are not correlated to the activity of the anterior amygdaloid area subpart ($p = 0.8$). Solid and dashed lines correspond to the significant and not significant linear regression lines, respectively.

Tables

Table 4-1. Differences between amygdala subparts in the collective impact of the variation in illuminance on their activity.

Main GLMM			
Effect	F Value (df)	P value*	Partial R^2
Amygdala subpart	4.79 (9,524)	**<.0001**	**0.07**
Task	27.93 (1,525)	**<.0001**	**0.05**
Amygdala subparts x stimulus type	0.97 (9,524)	0.4	
Age	1.18 (1,24)	0.28	
Sex	1.01 (1,24)	0.32	
BMI	0.17 (1,24)	0.68	

Table 4-2. Post hoc comparison of amygdala subparts

Pairwise comparisons			
Contrast#	t-value	$P_{uncorrected}$	$P_{corrected}$
1 vs. 2	0.09	0.92	1
1 vs. 3	2.2	0.02	0.45
1 vs. 4	-0.71	0.47	0.99
1 vs 5	2.54	0.01	0.24
1 vs 6	-0.69	0.49	0.99
1 vs 7	1.76	0.07	0.76
1 vs 8	-1.7	0.08	0.79
1 vs 9	1.88	0.06	0.68
1 vs 10	-1.25	0.21	0.96
2 vs 3	2.09	0.03	0.53
2 vs 4	-0.8	0.42	0.99
2 vs 5	2.44	0.01	0.3
2 vs 6	-0.78	0.43	0.99
2 vs 7	1.66	0.09	0.81
2 vs 8	-1.79	0.07	0.74
2 vs 9	1.78	0.07	0.74
2 vs 10	-1.34	0.18	0.94
3 vs 4	-2.89	0.004	0.10
3 vs 5	0.34	0.73	1
3 vs 6	-2.88	0.004	0.11
3 vs 7	-0.44	0.66	1
3 vs 8	-3.89	**0.0001**	**0.004**
3 vs 9	-0.29	0.77	1
3 vs 10	-3.45	**0.0006**	**0.02**
4 vs 5	3.24	**0.001**	**0.04**
4 vs 6	0.02	0.98	1
4 vs 7	2.46	0.01	0.29
4 vs 8	-0.99	0.32	0.99
4 vs 9	2.57	0.01	0.23
4 vs 10	-0.54	0.59	0.99
5 vs 6	-3.22	**0.001**	**0.04**
5 vs 7	-0.78	0.43	0.99
5 vs 8	-4.23	**<.0001**	**0.001**
5 vs 9	-0.63	0.53	0.99
5 vs 10	-3.79	**0.0002**	**0.006**
6 vs 7	2.44	0.01	0.30
6 vs 8	-1.01	0.31	0.99
6 vs 9	2.55	0.01	0.24
6 vs 10	-0.56	0.57	0.99
7 vs 8	-3.45	**0.0006**	**0.02**
7 vs 9	0.15	0.88	1
7 vs 10	-3.01	0.002	0.08
8 vs 9	3.55	**0.0004**	**0.01**
8 vs 10	0.46	0.64	1
9 vs 10	-3.11	0.001	0.06

Table 4-3. Statistical outputs of GLMM testing for differences between the activity of each subpart of the amygdala under each illuminance.

Main GLMM			
Effect	F Value (df)	P value*	Partial R^2
Task stimuli	17.68 (1,523)	**<.0001**	**0.03**
Illuminance	11 (4,2200)	**<.0001**	**0.02**
Amygdala subpart	1.63 (9,523)	0.10	
Illuminance x Task stimuli	4.66 (4,2200)	**0.001**	**0.008**
Task stimuli x Amygdala subpart	0.71 (9,523)	0.70	
Illuminance x Amygdala subpart	1.42 (36,2200)	**0.04**	**0.02**
Illuminance x Amygdala subpart X Task stimuli	0.51 (36,2200)	0.99	
Age	0.72 (1,24)	0.40	
Sex	0.2 (1,24)	0.65	
BMI	1.77 (1,24)	0.19	

Table 4-4. Post hoc contrasts between illuminances within each amygdala subpart. Illuminance is reported in mel EDI lux. Only significant comparisons are reported in the main text. For the full table, refer to **Appendix 3. Suppl Table 6-10**.

Pairwise comparisons			
Amygdala subpart	Contrast[#]	t-value	$P_{\text{-value}}$
3	0 vs 190	3.42	**0.005**
3	0.16 vs 190	4.15	**0.0003**
3	92 vs 190	3.51	**0.004**
5	0 vs 190	3.8	**0.001**
5	0.16 vs 190	3.89	**0.001**
5	37 vs 190	2.95	**0.02**
5	92 vs 190	3.3	**0.008**
7	0 vs 190	3.18	**0.01**
7	0.16 vs 190	2.79	**0.04**
9	0 vs 190	4.46	**<.0001**
9	0.16 vs 190	4.09	**0.0004**
9	37 vs 190	4.5	**<.0001**
9	92 vs 190	3.8	**0.001**

Discussion

Light therapy is recognized as being effective in treating several mood disorders. However, the underlying brain mechanisms involved have not been fully resolved, but it is likely to involve the amygdala (X. Huang et al., 2023). Considering the connection between the neural pathways involved in the regulation of mood and emotional processing (Price & Drevets, 2010), we aimed to determine which subpart of the amygdala was affected by light during the processing of auditory emotional stimuli. We found that the medial and superior regions of the amygdala showed a marked and linear reduction of activity with increasing illuminance, specifically when processing emotional stimuli. Furthermore, the activity of the AAA, in the superior part of the amygdala may be related to the behaviour during the task. These findings provide additional insight into the mechanisms that underlie the biological impact of light on the brain and may contribute to the benefits of light therapy in the treatment of mood disorders.

In rodents, the central and medial amygdala receives direct inputs from ipRGCs, and both regions have been implicated in the impact of light on anxiety-related behaviours (Delwig et al., 2016; Hattar et al., 2006; Vinkers et al., 2010; G. Wang et al., 2023). Previous neuroimaging research reported that light can influence the activity of the amygdala including during emotional processing, but without isolating the specific nuclei involved (McGlashan et al., 2021; Vandewalle et al., 2010). The atlas we used to separate the amygdala includes 10 subparts, (Tyszka & Pauli, 2016) including among others the central nucleus, the basomedial nucleus and the medial and cortical nuclei together as their boundaries are not well defined enough on MRI images to separate them (Tyszka & Pauli, 2016). We found that the basomedial and medial and cortical nuclei subparts show a decreased activation with higher illuminances.

In contrast, the central nucleus subpart activity does not significantly vary with changes in illuminance. Therefore, our results support that in humans, the medial nucleus rather than the central nucleus mediates the impact of light on emotional state. This provides support for the potential existence of a functional projection from ipRGCs to the medial part of the amygdala in humans, as previously demonstrated in rodents (Tri & Do, 2019). This further suggests that, similar to mice, light can influence emotional status independently of the hypothalamus suprachiasmatic nucleus (SCN), the site of the principal circadian clock that receives the strongest inputs from ipRGCs in rodents (Tri & Do, 2019). However, our data are not incompatible with an effect of light on the basomedial and medial nuclei activity through the SCN. Future connectivity analyses could help in choosing between these alternatives.

The basomedial and medial nuclei send reciprocal projections to each other and both project to the cortical nucleus (Whalen & Phelps, 2009). In addition, a simplified overview of the sensory information flow through the amygdala proposes that information enters through the basolateral nuclei and then progresses through to the central and medial nuclei which act as an output station for downstream targets (Šimić et al., 2021). If correct, our findings would mean that light affects emotional processing in the entry doors of sensory information the amygdala.

Activation of the medial nucleus is associated with stress and leads to the secretion of

adrenocorticotropic hormone and the activation of the hypothalamic–pituitary axis, i.e., a neuroendocrine system that maintains physiological homeostasis (Šimić et al., 2021). The medial nucleus mainly contains GABAergic neurons (McDonald & Augustine, 1993) suggesting that it fulfils its functions mainly through an inhibitory influence on downstream areas, within and outside of the amygdala. Based on our findings, one could postulate that light reduces or inhibits this influence. The hypothesis that ipRGCs have the potential to be inhibitory is not without evidence, as a rodent study found that a subset of ipRGCs release the inhibitory neurotransmitter GABA at brain targets (SCN, IGL, vLGN), leading to reduced sensitivity of the pupil to light and circadian photoentrainment (Sonoda et al., 2020).

Aside from the basomedial and medial/cortical subparts, we also find a significant impact of illuminance on the ATA, encompassing amygdalocortical area, amygdalohippocampal area, and periamygdaloid cortex, and AAA. Providing plausible interpretations for their responses is more complicated, as there is less research on these areas in comparison to the other amygdala nuclei. The amygdalohippocampal area, and the periamygdaloid cortex both receive projections from the basomedial and medial nucleus and project back to the medial nucleus (Whalen & Phelps, 2009). The AAA is less developed in primates and predominantly receives projections from the lateral and central nuclei (Šimić et al., 2021; Whalen & Phelps, 2009). Although we do not have empirical data to support this hypothesis, we tentatively speculate that given the high interconnectivity of the amygdala nuclei (Whalen & Phelps, 2009), the deactivation in the ATA and AAA in response to illuminance changes reflects a downstream propagation of signals from the output of the basomedial and medial/cortical nuclei. While the visualisation of the whole brain results over the entire sample supports a local decrease of activity over the area covered by all four subparts, it does not point toward one of them in particular. Ultimately, although we favour an impact of light on the amygdala through the direct projection of ipRGCs to the medial nucleus, all four subparts could equally contribute to the decreased BOLD signal detected under higher illuminance (Tri & Do, 2019).

We stress that the auditory emotional task used has been validated (Grandjean et al., 2005; Sander et al., 2005; Vandewalle et al., 2010) and was successful in triggering emotional responses, both at the level of behaviour and activity of the amygdala. Behavioural measures (i.e., reaction times) were, however, not significantly different across the short light exposure of different illuminance levels. We do find a nominal significant link between reaction times and the activity of the AAA, which is significantly affected by illuminance. However, based on this finding, it is unclear how longer light exposures may affect behavioural responses acutely and over an extended period.

Furthermore, a study in rodents investigated the brain regions modulated by the optokinetic reflex and found and inhibitory response in the amygdala (Macé et al., 2018). In humans, the processing of negative stimuli has been associated with increased activity in the amygdala whereas positive stimuli have been associated with decreased activity in the amygdala (Bartels & Zeki, 2000). A functional neuroimaging study that focused on bright light therapy in healthy young participants found that after three weeks of bright light intervention, there was a dose-dependent decrease in the response to emotional stimuli in the amygdala and the medial prefrontal cortex (Fisher et al., 2014). Our findings support that the reduced responsiveness of

(part of) the amygdala is already present acutely, during short light exposure and may be maintained after prolonged and repeated exposure to light. Light exposure may therefore be beneficial to the emotional state through an acute and prolonged reduction of the response of the basomedial and medial parts of the amygdala.

The amygdala sends several downstream projections including to the frontal cortex, which governs cognition. Also the basomedial and medial nuclei and the periamygdaloid cortex project to the frontal cortex (Whalen & Phelps, 2009). In addition, one of the main targets of the medial nucleus is the hypothalamus, over the anterior paraventricular nucleus, while the basomedial nucleus also projects to the hippocampus and the ventral striatum (Sah et al., 2003; Whalen & Phelps, 2009). Future research shall elucidate which of these projections modulates the impact of light on emotional processing and/or on the beneficial impact of light on emotional state.

The decrease of activity we find in several subparts of the amygdala contrasts with previous research done using 3T fMRI in healthy participants using the same emotional task. They found that, under blue monochromatic light, emotional stimuli increased the activity of the amygdala (Vandewalle et al., 2010). The conflicting findings may be due to the differences in light sources used as it was a monochromatic light in that previous study. In contrast, another resting-state 3T MRI study, that did not involve a cognitive task, found that the activity of the amygdala was decreased under polychromatic white light (~34.67 mel EDI lux; 2800k) in comparison to darkness (McGlashan et al., 2021). In the present study, we used a polychromatic white, blue-enriched light source of three different intensities (37, 92, 190 mel EDI; 6500k), i.e. the lowest light level we used has a similar mel EDI lux to the resting state study. It may be speculated that the amygdala increases or decreases its activity in response to light depending on the illuminance and spectrum, thus on the type of retinal photoreceptor recruited.

In terms of the photoreceptors involved, we cannot conclusively say that ipRGCs are solely responsible for the decreased activity found in the subparts of the amygdala at higher illuminance. Given the projection of ipRGCs to the medial nucleus of the amygdala reported in rodents and the light level we used, their involvement is plausible. However, rods and cones may also be involved and could be contributing at different illuminance levels (Spitschan, Reinhard, et al., 2021). Future studies in humans could determine the main photoreceptor involved in modulating the impact of light on emotion processing and emotional status by using metameric lights. Whilst the perception of the light would remain the same for the observer, the spectral characteristic of the light source would change allowing to selectively affect one photoreceptor type (Viénot et al., 2012).

Emotional regulation is vital and evolutionarily critical. The amygdala fulfils part of this regulation to allow adaptation to the changing environment. We find that several subregions of the amygdala, including the medial nucleus that receives direct projection from ipRGCs, showed a marked and approximately linear reduction in the activity as illuminance increased during the processing of emotionally charged stimuli. We speculate that it is through the medial nucleus that prolonged light exposure affects the emotional state in healthy individuals as well as in patients.

Discussion

General Discussion

The importance of our lighting environments has often been overlooked or viewed only through architectural perspectives, however, research over the past decades has established light as being central to our health and wellbeing (Boyce, 2022). The development of electrical lighting gave us greater control over our lighting environments than ever before and essentially freed us from the 24-hour light-dark cycle of the earth. The technical advances of light bulbs have developed rapidly, from the traditional incandescent and fluorescent light bulbs to the more energy-efficient light-emitting diode (LED) light bulbs (Pimputkar et al., 2009). As the technology for light bulbs advanced, the emission spectrums for our electrical lighting environments also changed. Incandescent and fluorescent light bulbs have an emission spectrum with a dominant wavelength closer to the classical visual spectrum (~550 nm) whereas the most common form of LED has a peak around 440–460 nm and a second broader peak in the yellow–green wavelength region (Lucas et al., 2014). The development of LEDs made light a flexible and controllable parameter, however, there is a high possibility of exacerbating light misuse and its negative impacts on human wellbeing. Aberrant light regimes can have adverse effects including sleep disturbances (Chellappa et al., 2013), cognitive impairments (Vandewalle et al., 2009), mood disorders (Bedrosian et al., 2013) and have also been associated with some cancer pathologies (Garcia-Saenz et al., 2018).

As stated throughout the thesis there are two light-sensitive systems in the human retina. The classical visual system is needed for visual perception and primarily relies on rods and cones photoreceptors and then the NIF or 'non-visual' system, which primarily relies on ipRGCs and detects environmental irradiances (Lucas et al., 2014; Wässle, 2004). The two systems are not completely separated with ipRGCs contributing to some visual functions (Allen et al., 2019; Brown et al., 2010, 2012) and rods and cones are required for complete NIF responses (Güler et al., 2008). Whilst the photoreceptors interact, the two systems do have different maximal photopic sensitivities with the classical visual system maximally sensitive towards yellow-green wavelength light (~550nm), whereas the NIF system is maximally sensitive to short blue wavelength light (~480nm) due to the expression of the photopigment melanopsin (Lucas et al., 2014; Provencio et al., 2000). The NIF system mediates light's influence on several neuroendocrine, and neurobehavioral functions, which are collectively termed NIF functions (Campbell, Sharifpour, & Vandewalle, 2023). These functions include circadian entrainment (Berson et al., 2002), melatonin suppression (Brainard et al., 2001), pupillary responses (Gamlin et al., 2007), influencing alertness and cognition (Gaggioni et al., 2014; Vandewalle et al., 2009) and mood (Legates et al., 2012).

Considering the wide range of NIF functions, it is clear that the brain wiring underlying this system is diverse and complex and investigations in rodent models have shown that ipRGCs innervate a wide range of brain regions (Tri & Do, 2019). Translating this research to humans is complicated and one of the main techniques to understand the brain regions involved in NIF functions in humans is neuroimaging. Previous neuroimaging studies in humans have demonstrated that light influences several brain regions, but this is dependent on the characteristics of the light source, cognitive activity, circadian phase and homeostatic sleep pressure (Campbell, Sharifpour, & Vandewalle, 2023). It is hypothesised that light influences the

subcortical regions of the brain before cortical activation, most likely dependent on ongoing cognitive processing (Gaggioni et al., 2014).

Advances in the understanding of the NIF system have proven that light can influence human physiological and psychological processes, this has led to lighting industries marketing integrative lighting solutions to benefit human health (Houser et al., 2020; Kompier et al., 2020). Integrative lighting aims to consider the visual and NIF aspects of light in order to maintain the visual acuity but also benefit human wellbeing through optimising the NIF impacts of light (Campbell, Sharifpour, & Vandewalle, 2023). A key organisation in the lighting field, Commission Internationale de l'Eclairage (CIE), has recommendations for workplace lighting to address health and wellbeing based on visual performance and has stated that the development of comprehensive recommendations that include the non-visual effects of light are needed and achieving this requires further research into the NIF system in humans (Veitch, 2023).

To achieve integrated lighting solutions fundamental questions about the NIF system at the brain level in humans still need to be answered. We utilised two techniques to address the main goals of the thesis, ultra-high-field 7 Tesla (7T) functional magnetic resonance imaging (fMRI), allowing for better visualisation of subcortical brain regions and infrared eye tracking system that allowed for pupil size measurements during the fMRI scans.

The overall goals of the thesis are centred on investigating the biological impacts of blue-enriched light on brain functions using 7T ultra-high field MRI and eye tracking. We conducted three main studies to address this goal. In the following sections, the main findings and conclusions of each chapter will be discussed in further detail.

The task-evoked pupil responses under different illuminances

In chapter two, we aimed to characterise the TEPR associated with auditory inputs, under different light levels during two cognitive tasks. We used eye-tracking data recorded from healthy young participants, who completed attentional and emotional auditory cognitive tasks during an fMRI recording whilst exposed to illuminance variation. As already well established we found that at higher light levels there is a smaller sustained pupil size (Beckers et al., 2023). When we looked specifically at the TEPRs to auditory stimuli, these were also larger at a higher illuminance (index by mel EDI). This finding was consistent across both cognitive tasks but there were some task-specific differences in the impact of illuminance on the different stimuli of the two cognitive tasks.

Moving on from what was discussed in the paper, the hypothesis that the moment-to-moment neural activity of the locus coeruleus (LC) can be determined through pupil size alone is an appealing notion. The most compelling evidence for the link comes from a primate study showing that natural and task-induced pupil size fluctuations can reliably reflect the neural activity of the LC (Joshi et al., 2016). However, this was not the only neural region linked to pupil fluctuations, the intermediate layers of the superior colliculus (SCi) have been implicated in pupil size control (Joshi et al., 2016; C. A. Wang et al., 2012).

There is a proposed pathway centred on the superior colliculus (SC) being a key region involved in changes in pupil diameter associated with cognitive processing (C. A. Wang & Munoz, 2015). The SC is involved in the visual pathway and can be separated functionally into the superficial (SCs) layers, which receive input from the retina and the primary visual cortex, and the SCi layers which receive motor and sensory inputs (May, 2006). The SCs also project to the SCi. Through key neural connections via inputs to the pupil control circuits the SC has the potential to modulate pupil size during cognitive processing, potentially through the parasympathetic and/or the sympathetic systems (C. A. Wang & Munoz, 2015).

Interestingly in rodents, ipRGCs project to the SC (Tri & Do, 2019) and if this was conserved in humans, the SC may potentially be involved in the NIF impact of light. Given that the SC has already been implicated in non-luminance fluctuations in pupil size (C. A. Wang & Munoz, 2015) and is innervated by ipRGCs, we could interpret the TEPRs results differently. The results therefore could be compatible with the hypothesis that the SC is a key brain region involved in the NIF impact of light on TEPRs. We cannot rule out the possible involvement of the SC or SC neural pathway in the presented TEPR results.

Overall, the LC is more consistently associated with fluctuations in pupil size and has been implicated in the NIF impacts of light (Joshi et al., 2016; Vandewalle et al., 2009). The SC is innervated by the LC and it has also been suggested that neural activity may be mediated through LC-arousal, this would include influencing the SCi activity, leading to changes in pupil size (Edwards et al., 1979; Joshi et al., 2016).

Furthermore, there is evidence that the relationship between the LC and the pupil can be dynamically modulated by brain states (Megemont et al., 2022). A recent paper investigated the link between the lateral hypothalamus (LH), the anterior cingulate cortex (ACC) and pupil size in rodent models. The ACC is another brain region known to be closely linked to pupil size regulation and receives projections from the LC (Joshi et al., 2016; Porrino & Goldman-Rakic, 1982). The LH also sends neural projections to the ACC and a further study found that pupil dilation could be caused in response to LH activation (Jin et al., 2016; Ranson & Magoun, 1933). LC-arousal state and pupil dynamics have also been reported to be modulated by LH activity (De Lecea, 2015; Hagan et al., 1999; Herrera et al., 2015). Overall, the study suggests that the activity of the LH can be correlated with pupil dynamics and ACC local field potential recordings. Suggesting that recording LH activity is a novel way to research the regulation of brain dynamic stages (Takahashi et al., 2023).

The LH has a key role in brain state regulation, especially for its involvement in sleep-wake regulation (Scammell et al., 2017). If we were to assume there was a similar relationship between LH activity and pupil dynamics seen in humans, we could hypothesise about the potential involvement of the LH in the TEPRs results presented. The LH is innervated by ipRGCs, and we could speculate that its activity would be modulated under different illuminance, which in turn would influence the pupil responses discussed in chapter two.

Overall, we cannot rule out the involvement of the SC and LH in TEPRs increasing under higher illuminance without MRI analysis. Interestingly in our next study, we focused on the hypothalamus and found that the posterior hypothalamus subpart (encompassing the LH) was activated under higher illuminance levels during two cognitive tasks.

Light illuminance and the human hypothalamus

In the second study, we look specifically at the subcortical circuitry underlying the stimulating impact of light on cognitive processes. Healthy young participants completed an fMRI scan to assess the impact of variations in light illuminance on the regional activity of the hypothalamus, whilst completing two auditory cognitive tasks. We found that for both the executive and emotional tasks, higher illuminance triggered an increase in activity over the posterior part of the hypothalamus and in contrast, evoked a decrease in activity over the anterior and ventral parts of the hypothalamus. Furthermore, the performance of the executive task was improved under higher illuminance and was negatively correlated with the activity of the posterior hypothalamus subpart. Overall, the results suggest that different hypothalamus regions underlie the impact of light on cognition and we hypothesize that light could act on the orexin and histamine systems to affect the quality of wakefulness.

The investigation's results did not confirm the original hypothesis that we had predicted. Instead of higher illuminance leading to an activation over the anterior hypothalamus subpart (encompassing the suprachiasmatic nucleus (SCN)), we found increased activation over the posterior subpart of the hypothalamus (encompassing the mamillary bodies (MB), the LH and tuberomammillary nucleus (TMN)).

Considering the LH which is innervated by ipRGCs and therefore can be directly influenced by variation in illuminance (Tri & Do, 2019). The LH is an important region in the orexin system which is crucial for maintaining wakefulness and has been proven to be involved in mood and emotional processing (Chen et al., 2021; Scammell et al., 2017). Orexin neuron activity is high during wakefulness and interestingly in rodents, photoactivation of orexin neurons leads to waking from sleep (Adamantidis et al., 2007; Scammell et al., 2017). We could hypothesise that the increasing activity of the posterior hypothalamus we see during both tasks is due to increased activity of the LH directly through its innervation by ipRGCs, which would then excite wake-promoting brain regions, including key regions such as the TMN, and LC (Scammell et al., 2017).

There is evidence of direct action of the LH orexin cells on the LC noradrenergic system. This signalling pathway would influence LC activity and therefore downstream cognitive processing (Horvath et al., 1999). We could suggest, at least for the emotional task, that the increased activity under higher illuminance would have a direct effect on the LC activity and potentially be involved in the TEPRs we investigated in chapter two. We did not investigate the TEPRs for the executive task because it is not a stream-of-events cognitive task that triggers a transient pupil response to stimuli, but this pathway may still be influenced.

An aspect of the investigation we were not expecting was to see a deactivation in the anterior part of the hypothalamus, which encompasses the SCN. In general, it is thought the ipRGCs mainly act through the release of the excitatory neurotransmitter glutamate. However, a subset of ipRGCs were found to release the inhibitory neurotransmitter GABA at key brain targets including the SCN, causing reduced sensitivity of the pupil light response and circadian photoentrainment in rodents (Sonoda et al., 2020). The majority of SCN neurons are γ-amino butyric acid (GABA)-ergic and exhibit excitatory and inhibitory characteristics which may depend on the circadian phase. Understanding the role of GABA in the SCN is complicated and has not

been fully resolved (Ono et al., 2018, 2021). However, here we could speculate that the influence of light on the SCN is through ipRGCs inhibition, which may propagate onto downstream areas within the hypothalamus and other brain regions.

We also found a behavioural link with the executive task and a partial link with the emotional task and the posterior hypothalamus subpart. This is in contrast to what is suggested by the literature. Neuroimaging studies have proven that short periods of light exposure (1<min) can influence cognitive brain functions (Vandewalle, Gais, et al., 2007; Vandewalle, Schmidt, et al., 2007). However, whether the modulation of key brain areas causes behavioural change is still debated (Lee et al., 2021; Lok et al., 2018). Generally, it is assumed that prolonged exposure to light is required to positively affect cognitive performance, alertness and reaction times (Alkozei et al., 2016; Silvani et al., 2022).

Emotional processing of the amygdala under different illuminances

In the final study, we aimed to determine the impact of light exposure on the activity of the amygdala during the processing of emotional stimuli. We used 7T fMRI to record the activity of the amygdala in healthy young adults exposed to light of various illuminances while engaged in an auditory emotional task. We found that several subparts of the amygdala show a marked reduction of activity under higher illuminance when processing emotionally charged stimuli.

Light's influence on mood can be split into two retina-brain light-sensitive pathways. The first is an SCN-dependent pathway that would act on mood through the modulation of biological rhythms, including influencing key regions involved in sleep-wake regulation. The second pathway would be an SCN-independent pathway including influencing mood through modulation of orexinergic pathways, and emotional processing pathways through limbic regions (Chen et al., 2021; Maruani & Geoffroy, 2022).

Here, we tested whether the medial or central nuclei of the amygdala could be modulated by the impact of light during emotional processing. The activity of the amygdala could be influenced by light through ipRGCs direct projections to the medial nucleus (Tri & Do, 2019) or may be influenced through indirect inputs via the SCN, and thalamic regions (pulvinar) (Fernandez et al., 2018; Vandewalle et al., 2010).

Light could influence key pathways already known to be involved in emotional processing. For example, a limbic-to-cortical circuit, involving the amygdala, the anterior cingulate cortex, and the medial prefrontal cortex (mPFC), is known to be important in modulating the reactivity to emotionally salient environmental stimuli (Phillips et al., 2003; Quirk & Mueller, 2007). Here, the propagation of the amygdala signal would move through the limbic structures before influencing the frontal cortex in modulating the emotional and cognitive response based on the external environment.

A limitation of the results presented is that we did not look at the possibility of lateralization in the amygdala mainly due to template constraints. There is evidence from functional neural

imaging studies on emotional processing that there is lateralized amygdala activity (Baas et al., 2004). Further analysis could look at the potential lateralization of the amygdala results.

Further purely explorative analysis for the emotional task included using the BDI (Beck, Steer, et al., 1988) and BAII (Beck, Epstein, et al., 1988) as covariates in the GLMMs for the fMRI task analysis. We wanted to see if the participant's subjective mood evaluation could be related to fMRI data. There were no significant results for this analysis, most likely due to the fact it was a healthy young population that was screened for mood disorders.

We did try exploratory connectivity analysis with the emotional task. A recently published study arising from the HILIGHT dataset found that blue-enriched light modulated the task-dependent information flow from the subcortical pulvinar region to the cortical intraparietal sulcus, both key regions involved in attentional regulation. The study provides important support that the NIF impact of light can influence ongoing cognitive activity through modulation of cross-talk between brain regions (Paparella et al., 2023).

We therefore hypothesised that there was a possibility of blue-enriched light influencing the crosstalk between brain regions in the emotional task. The separate investigations on the hypothalamus and amygdala found that subparts of both regions were influenced by illuminance in different ways, and we hypothesised that these regions could be part of the NIF brain pathway involved in emotional regulation.

As stated above light is thought to influence mood through two pathways an SCN-dependent and an SCN-independent pathways (Chen et al., 2021). The LH can potentially be involved in both pathways, as the LH can influence mood through modulation by the SCN or the LH may also be involved in mood regulation through orexinergic pathways independent of the SCN as the LH is innervated by ipRGCs and contains orexin neurons (Chen et al., 2021; Maruani & Geoffroy, 2022).

We used the posterior hypothalamus subpart that was activated under higher illuminance and tried exploratory psychophysiological interaction brain connectivity analysis. We found no conclusive evidence of brain connectivity between the posterior hypothalamus subpart and other brain regions in an emotional context. We did not take this analysis any further mainly due to time constraints. However, if we were to continue this line of investigation, we could look at the anterior part of the hypothalamus subparts that showed decreased activity under higher illuminance, similar to the decreased activity seen in the amygdala subparts, potentially probing the SCN-dependent pathway.

However, if we consider that the posterior hypothalamus subpart and amygdala are conclusively not effectively connected in the context of the emotional task. We could speculate that light is influencing the posterior hypothalamus and several subparts of the amygdala through separate emotional processing pathways.

Light could be influencing emotional processing by activating the orexinergic pathways (Maruani & Geoffroy, 2022). The orexinergic system is involved in modulating arousal and has been implicated in light's influence on the regulation of mood by affecting the dorsal raphe in rodent models (Adidharma et al., 2012; Nixon & Smale, 2007; Sakurai, 2007). In this task, under higher illuminances the orexin neurons in the LH would be activated, leading to the activation of wake-promoting nuclei through noradrenaline release by the LC.

A separate emotional pathway could be possible where light influences the activity of the amygdala through a pathway that involves ipRGCs and the amygdala (potentially with other regions- nucleus accumbens, perihabenular, hippocampus) leading to a decrease in activity or inhibition in these regions during emotional processing (Chen et al., 2021; Maruani & Geoffroy, 2022).

Finally, to suggest a reason in chapter two why we don't see a significant difference between emotional and neutral TEPRs, it may be due to the impact light has on emotional processing in the brain (Chen et al., 2021). As pupil dynamics are known to be influenced by brain states we could hypothesise that the emotional stimuli don't evoke stronger TEPRs in comparison to the neutral stimuli because of light's NIF influence on emotional processing, which is modulating the underlying neural activity that causes a TEPR. Therefore, the emotional auditory stimuli are less potent due to lights NIF impact on mood, potentially through modulating the activity of the amygdala.

Overview of Light Brain Connections

A more general overview of the three studies can be discussed in a scheme that describes how the NIF effects of light spread from the retina to the subcortical and cortical regions in humans. Evidence from previous human neuroimaging investigations led to the hypothesis that light first influences the subcortical regions of the brain involved in arousal regulation, before affecting cortical regions, depending on the ongoing cognitive processing (Gaggioni et al., 2014; Vandewalle et al., 2009). The proposed scheme suggested that light signal may reach the SCN in the hypothalamus and then the LC leading to widespread modulation of cortical activity depending on the cognitive context (Vandewalle et al., 2009).

In chapter three, we show the distinct local dynamics of hypothalamus regions that are affected by illuminance during short light exposure periods lasting 30 to 50 seconds. The executive task used was an N-back task (0-back and 2-back) where participants hear a series of auditory letters and are required to state for each letter if it is the same to the letter presented *n* letters earlier (Cohen et al., 1997). This task recruits executive function, needed for auditory processing, attention, and updating and comparison of letters in working memory (Collette et al., 2006). This provides support for a very early role for the hypothalamus in mediating the stimulating impact of light on cognition in general.

Our results contrast with previous studies investigating the hypothalamus. A PET study found a decrease in activity in proportion to prior light exposure, in a region encompassing the SCN (Perrin et al., 2004). A neuroimaging study at 3T MRI using the same emotional task as in the HILIGHT protocol found an increase in activity over the posterior hypothalamus during exposure to blue monochromatic light in response to emotional stimuli in SAD patients compared to healthy controls (Vandewalle, Hébert, et al., 2011). Furthermore, a following 7T MRI study found a decrease in activity in the anterior part of the hypothalamus encompassing the SCN during exposure to different monochromatic light conditions (Schoonderwoerd et al., 2022). Our results add to what has previously been reported, proving evidence that there is both a decrease and

increase in activity that takes place in the hypothalamus in response to illuminance during an executive and emotional task. The contrasting results seen between studies may be due to several differences, higher resolution MRI imaging, different light characteristics and exposure times and the different protocols between studies. Overall, a better understanding of light's influence on the hypothalamus is needed but remains challenging due to the fact there are several light-sensitive nuclei of the hypothalamus and separating these areas by neuroimaging remains difficult.

In chapter two we investigated the pupil data, showing that TERPs are influenced by 30 to 50 s of repeated light exposure during an attentional task (oddball) and an emotional task. The emotional task has also been reported to trigger emotional responses that were in part independent of the attention focus on the stimuli (Grandjean et al., 2005). Considering the tight link between LC activity and TERPs reported in animal studies (Joshi et al., 2016), we consider that these results support that there is an early impact of light on the LC and the modulation of LC activity could mediate the initial impact of light on brain functions over several aspects of cognition. This would support the earlier observation reported by Vandewalle et al (2007) that there was increased activity in a brainstem area compatible with the LC during exposure to blue monochromatic light compared to violet monochromatic light (Vandewalle, Schmidt, et al., 2007). However, as previously mentioned in the discussion the LH, is also linked with the LC and has been associated with variation in pupil size (Takahashi et al., 2023). Our pupil data could therefore be considered as a support for the early role of the hypothalamus in mediating the impact of light, potentially, jointly with the LC.

The proposed scheme also suggested that light could swiftly affect limbic areas (Vandewalle et al., 2009). We confirm this view and narrow it down to a specific part of the amygdala including the following nuclei, the basomedial nuclei, the medial and cortical nuclei, the amygdala transition area (composed of amygdalocortical area, amygdalohippocampal area, periamygdaloid cortex) and the anterior amygdaloid area. Similar to the hypothalamus, neuroimaging studies Vandewalle et al (2007) and Vandewalle et al (2010) both done at 3T MRI and with healthy participants found an increase in amygdala activity in response to light onset. Vandewalle et al (2007) reported that at light onset, blue monochromatic light increases the activity of the right amygdala in comparison to green monochromatic light (Vandewalle, Schmidt, et al., 2007). Vandewalle et al (2010) reported increased activity of the amygdala to emotional stimuli under blue monochromatic light in comparison to green monochromatic light, using the same emotional task we utilised in the HILIGHT study (Vandewalle et al., 2010). This is in contrast to the decrease in amygdala activity that we observe during light exposure. The reported increase of amygdala activity for both neuroimaging studies was however mostly detected at light's onset. In addition, a 3T resting state MRI study found a decrease in amygdala activity during polychromatic white light in comparison to darkness (McGlashan et al., 2021).

Vandewalle et al (2010) also reported increased connectivity between the amygdala and the hypothalamus for the emotional response between blue and green light exposure. This aspect has not yet been investigated in our HILIGHT study (Vandewalle et al., 2010). The decreased activity in a part of the amygdala that we report does not mean that its connectivity with the hypothalamus may not also be strengthened. Similar to the hypothalamus study, discrepancies

between the studies may arise from the higher resolution MRI imaging, different light characteristics and exposure times and the different protocols between studies.

Overall, it can be suggested that our results support an early role for the hypothalamus, LC and amygdala in mediating the influence of light on brain function and cortical activity will likely be dependent on the cognitive context. The proposed scheme is based on the results presented in the thesis and evidence from previous light studies, but further light investigations in different age groups and at different times of the day may add to the complexity of the scheme.

Limitations

As in any research study, the protocol and methods we chose have certain limitations that should be addressed. One of the main limitations of all the studies presented in the thesis is that we cannot conclusively say which of the light-sensitive photoreceptors of the human retina are driving the NIF responses discussed. The light sources used for all three studies were a polychromatic white LED light source of three different intensities (blue-enriched light; 37, 92, 190 mel EDI lux; 6500 K) and a monochromatic orange light source (0.16 mel EDI lux; 589mn). Several of the previous neuroimaging studies in humans have used monochromatic light sources, which allows for better prediction of the photoreceptors contributing to NIF effects (Vandewalle, Archer, et al., 2011; Vandewalle et al., 2009, 2010). Research in humans however remains limited by the fact that one cannot knock out easily a photoreceptor system in a healthy individual, at least not as one can do in rodents for instance.

The LED light source was chosen for the project because it is a more realistic light source to what is used and encountered by individuals outside of a controlled lab environment. LEDs are one of the most common forms of lighting due to their cheap production and environmental advantages over traditional light sources (Houser et al., 2020). In addition, the choice of light conditions for the HILIGHT project was limited by technical aspects, we based the decision on what was available currently at the lab. We also needed to take into consideration what would be tolerated by participants in the scanner as participants needed to keep their eyes open for the entire MRI scan. Therefore, we couldn't use very high light intensity which would be uncomfortable or painful for participants to be exposed to for a long period of time. The intensity of the light conditions was in line with what has been previously used in past neuroimaging studies investigating light in humans (Daneault et al., 2014; Vandewalle, Archer, et al., 2011; Vandewalle et al., 2010; Vandewalle, Schmidt, et al., 2007).

Throughout the thesis the light conditions are discussed in terms of mel EDI lux as it has been proven that melanopsin-ipRGCs are the main retinal photoreceptor required for driving NIF functions, however, the classical photoreceptors are needed for a complete NIF response in rodent models (Güler et al., 2008). The situation is likely to be the same in humans so ipRGCs and cones (and maybe rods) are most likely contributing to the responses we report in the thesis.

Based on the literature, we privilege ipRGCs as being the main driver of the NIF effects described in the thesis. First, the hypothalamus and amygdala, which were the focus of chapters three and four, receive direct projection from ipRGCs based on rodent studies (Tri & Do, 2019). In addition,

previous research showed that blind individuals with (most likely) intact ipRGCs but no functional rods and cones still displayed intact NIF responses to light when considering subjective and objective measures of vigilance, and melatonin suppression and also in a neuroimaging study with a similar setting to the study of the presented thesis (Czeisler et al., 1995; Vandewalle et al., 2013; Zaidi et al., 2007). In addition, other neuroimaging studies have proven that the spectral composition of the light is important for brain activation with blue monochromatic light exposure leading to a larger impact on brain activity (Vandewalle et al., 2009, 2010; Vandewalle, Schmidt, et al., 2007). One neuroimaging study further reported ipRGCs-driven brain responses through the use of metameric light (Tow et al., 2017).

In line with melanopsin-ipRGCs being the primary photoreceptor of light's NIF impact, a meta-analysis study found that the best predictor for melatonin suppression at light levels above 21 photopic lux was mel EDI lux (Giménez et al., 2022). This meta-analysis is in line with several published studies and was further reinforced recently in a study confirming the main role of melanopsin-ipRGCs in mediating several NIF functions (circadian melatonin phase delays, melatonin suppression, subjective sleepiness, psychomotor vigilance, or sleep) finding that the blue-yellow opposing colour circuits of cones were physiologically relevant to these circadian NIF functions (Blume et al., 2023; Santhi et al., 2012). Whilst ipRGCs are most likely the main driver of NIF responses to light, the potential contribution of S-cones remains debated. S-cones present a peak sensitivity of around 420nm, which is close to the intrinsic sensitivity of ipRGCs and the NIF system (Lucas et al., 2014; Wässle, 2004). A study found that S-cones contribute to melatonin suppression, whereas a further study found no role for S-cones in NIF neuroendocrine and alerting responses (Brown et al., 2021; Spitschan et al., 2019).

The classical visual photoreceptors are known to contribute to the PLR at continuous and lower light intensities, however, ipRCGs contribute at higher light intensities and sustain the PLR for a longer period (Gooley et al., 2012). Therefore, we could hypothesise that the increase in TEPRs we see across the two cognitive tasks may be due to the recruitment of different photoreceptors at different light intensities. The classical photoreceptors could contribute more at lower light levels, whereas the increase in TEPRs at higher light levels could be due to the involvement of ipRGCs and the propagation of ipRGCs signalling to the LC and potentially other brain areas.

Lastly, rods have a peak at 507nm sensitivity and are mainly involved in scotopic night vision. They were most likely saturated at most of the light levels we used in the protocol and are less likely to contribute to our results. Yet, rods may contribute to circadian entrainment in rodents over a large range of illuminance, i.e. larger than for their role in vision (Altimus et al., 2010). Therefore, we cannot conclusively rule out the contribution of rods and cones to the presented results. Given, that the photopic EDI values for the light conditions used in the HILIGHT study are highly correlated, we cannot contribute all of the effects discussed solely to the contribution of melanopsin-ipRGCs.

Another, aspect of the light sources we have not considered over the three experiment chapters is that our light conditions did not only differ in terms of illuminance but also in terms of colours, the lowest illuminance consisted of a monochromatic orange light (0.16 mel EDI lux; 589mn) whereas the other was a blue-enriched white light. The orange light was initially used as a control that was aimed at removing visual responses from the responses we would detect under the blue-enriched light, as ipRGCs are (almost) insensitive to it. We decided in the end, to analyse

the data differently than initially thought and consider only the illuminance measured by mel EDI lux. In our view, this does not invalidate our findings as ipRGCs are the main photoreceptor through which NIF functions are mediated and mel EDI lux is the best metric used to report on how light sources impact melanopsin-ipRGCs (Altimus et al., 2008; Spitschan et al., 2018).

However, the melanopsin photopigment is a dual-state photopigment meaning that it can exist in two stable photoabsorption states, where phototransduction and chromophore regeneration are driven by photons of different wavelengths. Whereas the classical photoreceptors rely on an enzymatic cycle for chromophore regeneration and photons drive phototransduction (Melyan et al., 2005; Sexton et al., 2012; Terakita et al., 2008). Although the exact wavelengths are not settled (Terakita et al., 2008), longer wavelength light (590-620nm) was found to be the most efficient at driving chromophore regeneration in rodent models and humans leading to an increase in photosensitivity of ipRGCs (Mure et al., 2007, 2009). Furthermore, a study has provided evidence that mammalian melanopsin may have three states, which accounts for melanopsin-ipRGCs ability to sustain signalling over minutes and integration over wavelengths (Emanuel & Do, 2015). Interestingly, a neuroimaging study found that 1-hour pre-exposure to orange (~590nm) compared to short wavelength light increased the subsequent impact of light on executive brain responses (Chellappa et al., 2014). Implying that prior light history influences the NIF impact of light on cognitive brain activity. However, it is unclear whether the alternation between longer and shorter wavelengths could affect the sensitivity to one or the other wavelength. Attempts to combine both shorter and longer wavelength light to increase the NIF impact of light were unsuccessful (Papamichael et al., 2012). The isolation of the prior light history effect may require particular conditions (e.g. prolonged complete darkness between prior light and test light – personal communication of H. Cooper to G. Vandewalle).

We have also focused on short light exposure periods (<1 min), viewing long-term light exposure within the MRI is complicated due to limitations on how long participants can spend within the scanner. However, we could suggest a protocol where participants complete an fMRI scan exposed to one light condition continuously and then a second exposed to another light condition, before comparing the data.

A recent publication from the HILIGHT project investigated the potential bias induced by using repeated sequential short-light exposure by investigating the pupil light reflex (PLR). The results suggested that there could be a carry-over effect from one light period to another. The analysis found that the sustained PLR was stable over the higher irradiance levels (92, 190 mel EDI lux) but at lower irradiances (0.16, 37 mel EDI lux) the sustained PLR decreased from the first to ending block. Overall, the study suggests that along with the cognitive context previous light exposure influenced the PLR response.

If we consider these papers together - ((Beckers et al., 2023; Chellappa et al., 2014)- we can conclude that short-term prior light history may have potentially biased the results presented in the thesis. Retinal photoreceptors and their underlying neural circuits adapt to optimise their sensitivity during light exposure to the ambient light level (Lucas et al., 2012). It could be speculated that the results presented at lower light levels may have an induced bias due to the adaption of rods and cones. The use of eye-tracking data in the analyses of fMRI data may be a way forward to account for this potential bias.

It calls into question how we should control for a participant's light history before fMRI protocols. Melanopsin-ipRGCs photoreception is the main driver of NIF responses to light under high light levels which is not similar to the dim light adaption used in the protocol (Lucas et al., 2012). In the HILIGHT protocol we implemented, 5 mins of bright (1000 lux) light exposure followed by 45 min under dim light (< 10 lux). Future studies could modify this and use higher ambient light levels. If we consider the literature, the best way to isolate ipRGC contribution may be to avoid prior history in dim light (Giménez et al., 2022; Lall et al., 2010). Future investigations could simplify the light standardization period by using a higher ambient light level.

In the study looking at TEPRs, we could only include a relatively small sample size (attentional task, N=14; emotional task, N=15) in comparison to the other two studies. This was mainly due to technical issues with the infrared eye-tracking system. The MR-compatible infrared eye tracking system recorded the right pupil and was positioned behind the MRI head coil. The eye tracker was correctly positioned and calibrated for each participant before the participant was placed in the scanner. We could not readjust or restart scans if the eye tracker lost focus during the scanning. This often meant we lost data for multiple cognitive tasks as the eye tracker could lose focus early on in the fMRI scan. To conclusively link the assumptions, made in the study about the recruitment of the LC in the stimulating impact of light on TEPRs we need to analyse the MRI data acquired simultaneously with on focus on the brainstem (which is the work of one of my colleagues).

The ultra-high-field 7T MRI used in the study provides a higher resolution and high signal-to-noise data in comparison to 3T MRI allowing for better imaging of subcortical brain regions (Weiskopf et al., 2015). However, we required a higher number of participants to replicate the results seen at 3T MRI. We would attribute this to single-voxel-wise correction over the entire brain, the higher number of voxels at 7T MRI meant that reaching a significance level was more difficult due to multiple comparisons. Therefore, linking the TEPR results to the MRI data collected simultaneously would be difficult if we were to use whole-brain analysis. Region of interest analysis may be possible if we focus on the LC. My colleague is working on creating a mask for the LC area, therefore we could use that LC mask to extract activity estimates and do GLMM analysis with the averaged TEPRs under different light conditions.

Also, for this reason in chapters three and four, we chose to focus on regions of interest rather than using whole-brain analyses. In chapters three and four when we investigated the hypothalamus (Billot et al., 2020) and the amygdala (Tyszka & Pauli, 2016), we used brain templates to reliably subdivide the brain regions and extract the activity estimates. Both investigations are limited by the specificity of the template used. Whilst, 7T MRI provides higher resolution for neuroimaging, there are still limitations to accurately achieving nucleus resolution over both the hypothalamus and the amygdala. For the hypothalamus different nuclei of the hypothalamus do not have clear contrast boundaries based on MRI signals (Billot et al., 2020). Similarly, the amygdala can be subdivided into some nuclei but other nuclear regions were combined due to a lack of clear contrast boundaries based on MRI images (Tyszka & Pauli, 2016). This limits both studies as we can only hypothesise plausible scenarios based on the known literature. Future research would need to test the proposed mechanisms starting with rodent models.

Another aspect of mood and cognition that was not taken into account in the presented research is the possible influence of seasonality. For the recruitment of participants, we tried to consistently recruit participants across all the seasons, so the results were not influenced by the possible influence of seasonality. However, due to complications with COVID lockdowns and restrictions in Belgium, we were only able to start recruitment in December 2020 and the final participant used in this analysis was scanned in May 2023. In total 40 participants passed the initial screening but not all successfully completed the protocol and some acquired MRI data sets failed the quality control check. Seasonality is known to play a role in several mood disorders and has been proven to influence cognitive brain functions (Meyer et al., 2016; R. Zhang & Volkow, 2023). As we have not taken into account the seasonality in the analysis, we cannot rule out the potential bias that may be presented in the results. This may be specifically important for the presented result on the amygdala and emotional processing, a clarifying step for this investigation would be to include seasonality as a covariate in the analysis (Meyer et al., 2016).

Future research

The results presented in the thesis are only part of the ongoing HILIGHT project, therefore the existing dataset and the ongoing subprojects may answer some of the additional questions and limitations already discussed.

When we view only the presented results in the thesis, we can summarise the next planned steps as follows. For the TEPRs study discussed in chapter two, we aim to increase the eye-tracking sample size and investigate our hypothesis that it is the LC involved in the NIF response. For the hypothalamus and amygdala studies discussed in chapters three and four, we plan to do connectivity analysis within both regions, to investigate if the subparts are connected. For the hypothalamus, this analysis has already been started by my colleague. For the emotional task, further connectivity analysis could investigate if the deactivated anterior subparts of the hypothalamus and the medial amygdala subpart are effectively connected.

Furthermore, the HILIGHT project will assess the potential modulatory impact of certain environmental factors (time of day and sleep loss). Previous research has shown that the NIF impact of light on cognitive brain activity changes with time of day and sleep loss (Vandewalle, Archer, et al., 2011). Here, we will look at how the fMRI acquisitions will vary from morning to evening. For the sleep loss section, we will use actigraphy to get prior sleep-wake history and see whether sleep duration influences responses to light. Hypothesising that the NIF impact of light on brain activity will increase in the morning compared to the evening and in participants with shorter sleep durations (Vandewalle, Archer, et al., 2011).

The HILIGHT project has currently focused on a healthy young population (20-35y) but there is evidence of the NIF impact of light on cognition changing with age (Daneault et al., 2018). Specifically, teenagers (15-18y) tend to be a later chronotype and have high sleep needs. Therefore, they may be vulnerable to the negative impacts of light in the evening, especially due to social restrictions requiring teenagers to be at school early in the morning (Ricketts et al., 2022). Twenty teenagers completed the fMRI assessment in the evening and the acquired data will be compared to the young population (who also completed an evening scan). It was decided that teenagers would be scanned in the evening due to the critical impact light has on sleep in

teenagers (Ricketts et al., 2022). Furthermore, we plan on recruiting older adults (60-75y) to complete the fMRI assessments, as ageing appears to modify the NIF impacts of light (Daneault et al., 2014, 2016, 2018). Adapting lighting environments for the elderly population would be a non-invasive way to support health and wellbeing if specialised lighting was present in hospitals, and care homes (Geerdinck et al., 2016). Here, we hypothesise that brain activity will be increased when comparing teenagers to young adults and older adults.

Furthermore, exploratory analysis for the project could focus on sex differences. There is some evidence that light's NIF impact and perception are affected by sex differences (Chellappa et al., 2017). Beyond the investigations that have already been planned for the HILIGHT project, any planned future studies should take into account the limitations already discussed. An important next step for future neuroimaging studies will be through the use of metameric light sources, by varying the wavelength composition, metameric lights can target a specific photoreceptor type (Viénot et al., 2012). Allowing for the isolation of activity or pupil responses directly dependent on melanopsin-expressing ipRGCs.

Specifically, if we wanted to look at how mood is modulated by long-term light exposure in a neuroimaging protocol. We could develop a protocol where participants complete two fMRI protocols, before and after completing a bright light therapy protocol. This may further elucidate how emotional processing changes during light therapy. This could be done with healthy participants or with participants diagnosed with a mood disorder.

Conclusion

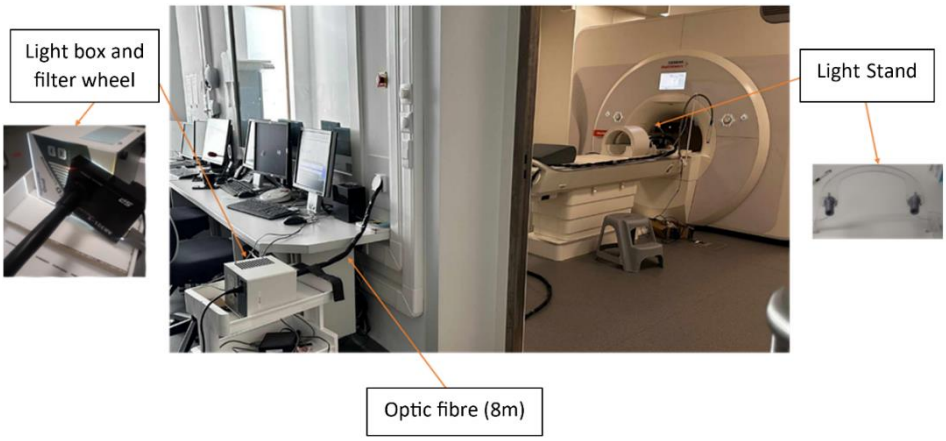
In conclusion, the presented research provides additional insight into the complex impact our light environments can have on our brain activity. The research provides a deeper understanding of the NIF impact of light on brain functions and has established a foundation for future research. Despite the limitations of our research, it is a step forward in unravelling the complex mechanism that underlies light's impact on brain activity.

The results presented in the thesis focus on single brain regions but for a complete understanding of the NIF impacts of light, a better elucidation of brain networks is needed. In a much broader context, the presented research can be viewed as a step towards the aim of developing scientifically-backed integrative lighting and may have important implications for everyday light environments (work, home), and the application of light as a therapeutic treatment.

Appendices

Appendix 1.

Supplementary figure for Chapter 2.



Supplementary Figure 6-1. MRI-compatible light system.

An 8-m long MRI-compatible dual-branched optic fibre transmitted light from a light box that was stored in the MRI control room. The dual end of the optic fibre was attached to a light stand fitted at the back of the MRI coil. A filter wheel and optical fibre filters (a monochromatic orange light filter (589mn; full width at half maximum: 10 nm) and a UV long bypass (433 – 1650nm) filter) were used to create the light conditions needed for the experiment.

Appendix 2.

Supplementary Tables for Regional response to light illuminance across the human hypothalamus.

Supplementary Table 6-1. Demographics of study sample.

	Total Sample	Executive Task	Emotional Task
Number of Participants	30	26	26
Age	24.2 ± 2.9	24.3 ± 3.0	24.4 ± 3.0
Sex (M)	11	10	10
Mood (BDI-II)	7.5 ± 7.0	6.7 ± 6.0	8.0 ± 7.3
Anxiety (BAI)	5.0 ± 4.1	4.8 ± 3.8	5.1 ± 4.3
Sleep quality (PSQI)	4.0 ± 2.6	3.7 ± 2.5	4.0 ± 2.7
Seasonality (SPAQ)	1.1 ± 0.8	1.2 ± 0.8	1.2 ± 0.8
Chronotype (HO)	48.7 ± 8.0	48.9 ± 8.2	48.7 ± 7.8
Daytime sleepiness (ESS)	6.5 ± 3.0	6.3 ± 3.0	6.2 ± 3.0
Years of Education	14.5 ± 3.1	14.5 ± 3.2	14.2 ± 3.2
Sleep duration (night before fMRI protocol – sleep diary based)	7.9 ± 0.7	7.8 ± 0.7	7.9 ± 0.7

Total number of participants who completed the study, and the number of participants included for each task (some participants had missing/corrupted data, see methods). BDI-II, Beck's Depression Inventory; BAI, Beck Anxiety Inventory; PSQI, Pittsburgh Sleep Quality Index; SPAQ, Seasonal Pattern Assessment Questionnaire; HO, Horne and Östberg; ESS, Epworth Sleepiness Scale. Refer to the method for the references to the scales and questionnaires.

Supplementary Table 6-2. Light Characteristics

	Low BEL	Mid BEL	High BEL	Orange
Lux	47	116	240	7.5
Peak Spectral Irradiance (nm)	460	460	460	590
Melanopic EDI (lux; ipRGCs)	37	92	190	0.16
Rhodopic EDI (lux; Rods)	39	97	201	0.94
Cyanopic EDI (lux; S-cones)	32	79	163	0
Chloropic EDI (lux; M-cones)	44	110	227	5
Erythropic EDI (lux ; L-cones)	46	113	233	8
Irradiance ($\mu W/cm^2$)	15	36	75	1.4
Photon flux($1/cm^2/s$)	4.12E+13	1.02E+14	2.10E+14	4.24E+12
Log Photon Flux (log_{10} ($1/cm^2/s$)	13.61	14.01	14.32	12.63
Narrowband peak	-	-	-	589
Narrowband FWHM	-	-	-	10

Detailed characteristics of the four conditions used in fMRI protocol. Blue enriched (BEL) (low, mid, and high) and monochromatic (589nm). ipRGCs: intrinsically photosensitive retinal ganglion cells. FWHM: full width at half maximum.

Supplementary Table 6-3. Post hoc contrasts between illuminances within each hypothalamus subpart during the executive task.

Hypothalamus subpart	illuminance	vs. illuminance	t-value	p-value
1 (inferior-anterior)	0	0.16	2.43	**0.0151**
1 (inferior-anterior)	0	37	2.59	**0.0098**
1 (inferior-anterior)	0	92	1.65	0.0993
1 (inferior-anterior)	0	190	3.30	**0.0010**
1 (inferior-anterior)	0.16	37	0.17	0.8683
1 (inferior-anterior)	0.16	92	-0.78	0.4330
1 (inferior-anterior)	0.16	190	0.86	0.3886
1 (inferior-anterior)	37	92	-0.95	0.3445
1 (inferior-anterior)	37	190	0.69	0.4892
1 (inferior-anterior)	92	190	1.65	0.0999
2 (superior-anterior)	0	0.16	0.79	0.4313
2 (superior-anterior)	0	37	0.76	0.4480
2 (superior-anterior)	0	92	1.37	0.1722
2 (superior-anterior)	0	190	1.15	0.2520
2 (superior-anterior)	0.16	37	-0.02	0.9810
2 (superior-anterior)	0.16	92	0.58	0.5628
2 (superior-anterior)	0.16	190	0.36	0.7198
2 (superior-anterior)	37	92	0.60	0.5490
2 (superior-anterior)	37	190	0.38	0.7036
2 (superior-anterior)	92	190	-0.22	0.8259
3 (posterior)	0	0.16	-1.32	0.1873
3 (posterior)	0	37	-1.22	0.2240
3 (posterior)	0	92	-2.14	**0.0323**
3 (posterior)	0	190	-2.35	**0.0190**
3 (posterior)	0.16	37	0.10	0.9180
3 (posterior)	0.16	92	-0.82	0.4101
3 (posterior)	0.16	190	-1.03	0.3037
3 (posterior)	37	92	-0.93	0.3542
3 (posterior)	37	190	-1.13	0.2578
3 (posterior)	92	190	-0.21	0.8375
4 (inferior-tubular)	0	0.16	2.15	**0.0316**
4 (inferior-tubular)	0	37	2.21	**0.0271**

Hypothalamus subpart	illuminance	vs. illuminance	t-value	p-value
4 (inferior-tubular)	0	92	2.80	**0.0052**
4 (inferior-tubular)	0	190	3.27	**0.0011**
4 (inferior-tubular)	0.16	37	0.06	0.9518
4 (inferior-tubular)	0.16	92	0.65	0.5176
4 (inferior-tubular)	0.16	190	1.12	0.2624
4 (inferior-tubular)	37	92	0.59	0.5575
4 (inferior-tubular)	37	190	1.06	0.2891
4 (inferior-tubular)	92	190	0.47	0.6356
5 (superior-tubular)	0	0.16	0.01	0.9882
5 (superior-tubular)	0	37	0.84	0.3986
5 (superior-tubular)	0	92	0.86	0.3920
5 (superior-tubular)	0	190	0.58	0.5604
5 (superior-tubular)	0.16	37	0.83	0.4069
5 (superior-tubular)	0.16	92	0.84	0.4002
5 (superior-tubular)	0.16	190	0.57	0.5704
5 (superior-tubular)	37	92	0.01	0.9905
5 (superior-tubular)	37	190	-0.26	0.7934
5 (superior-tubular)	92	190	-0.27	0.7842

Supplementary Table 6-4. Post hoc contrasts between illuminances within each hypothalamus subpart during the emotional task.

Hypothalamus subpart	illuminance	vs. illuminance	t-value	p-value
1 (inferior-anterior)	0	0.16	-1.19	0.2324
1 (inferior-anterior)	0	37	1.29	0.1979
1 (inferior-anterior)	0	92	2.03	**0.0431**
1 (inferior-anterior)	0	190	2.25	**0.0248**
1 (inferior-anterior)	0.16	37	2.48	**0.0132**
1 (inferior-anterior)	0.16	92	3.22	**0.0013**
1 (inferior-anterior)	0.16	190	3.44	**0.0006**
1 (inferior-anterior)	37	92	0.74	0.4616
1 (inferior-anterior)	37	190	0.96	0.3379
1 (inferior-anterior)	92	190	0.22	0.8243
2 (superior-anterior)	0	0.16	-0.14	0.8910
2 (superior-anterior)	0	37	1.14	0.2539
2 (superior-anterior)	0	92	2.86	**0.0043**
2 (superior-anterior)	0	190	3.49	**0.0005**
2 (superior-anterior)	0.16	37	1.28	0.2013
2 (superior-anterior)	0.16	92	3.00	**0.0028**
2 (superior-anterior)	0.16	190	3.63	**0.0003**
2 (superior-anterior)	37	92	1.72	0.0853
2 (superior-anterior)	37	190	2.35	**0.0190**
2 (superior-anterior)	92	190	0.63	0.5310
3 (posterior)	0	0.16	-1.24	0.2151
3 (posterior)	0	37	0.13	0.8954
3 (posterior)	0	92	-0.15	0.8799
3 (posterior)	0	190	-2.17	**0.0299**
3 (posterior)	0.16	37	1.37	0.1704
3 (posterior)	0.16	92	1.09	0.2763
3 (posterior)	0.16	190	-0.93	0.3506
3 (posterior)	37	92	-0.28	0.7775
3 (posterior)	37	190	-2.31	**0.0213**
3 (posterior)	92	190	-2.02	**0.0433**
4 (inferior-tubular)	0	0.16	0.06	0.9486
4 (inferior-tubular)	0	37	1.01	0.3134

Hypothalamus subpart	illuminance	vs. illuminance	t-value	p-value
4 (inferior-tubular)	0	92	2.54	**0.0113**
4 (inferior-tubular)	0	190	2.42	**0.0155**
4 (inferior-tubular)	0.16	37	0.94	0.3454
4 (inferior-tubular)	0.16	92	2.47	**0.0135**
4 (inferior-tubular)	0.16	190	2.36	**0.0185**
4 (inferior-tubular)	37	92	1.53	0.1262
4 (inferior-tubular)	37	190	1.42	0.1571
4 (inferior-tubular)	92	190	-0.11	0.9087
5 (superior-tubular)	0	0.16	0.04	0.9679
5 (superior-tubular)	0	37	1.85	0.0651
5 (superior-tubular)	0	92	1.71	0.0870
5 (superior-tubular)	0	190	1.10	0.2713
5 (superior-tubular)	0.16	37	1.81	0.0711
5 (superior-tubular)	0.16	92	1.67	0.0946
5 (superior-tubular)	0.16	190	1.06	0.2892
5 (superior-tubular)	37	92	-0.13	0.8939
5 (superior-tubular)	37	190	-0.75	0.4558
5 (superior-tubular)	92	190	-0.61	0.5403

Supplementary Table 6-5. Post hoc contrasts between hypothalamus subpart for each illuminance during the executive task.

Illuminance	subpart	vs. subpart	t-value	p-value
0	1 (inferior-anterior)	2 (superior-anterior)	1.25	0.2106
0	1 (inferior-anterior)	3 (posterior)	1.95	0.0511
0	1 (inferior-anterior)	4 (inferior-tubular)	0.37	0.7084
0	1 (inferior-anterior)	5 (superior-tubular)	0.84	0.4038
0	2 (superior-anterior)	3 (posterior)	0.70	0.4840
0	2 (superior-anterior)	4 (inferior-tubular)	-0.88	0.3798
0	2 (superior-anterior)	5 (superior-tubular)	-0.42	0.6763
0	3 (posterior)	4 (inferior-tubular)	-1.58	0.1147
0	3 (posterior)	5 (superior-tubular)	-1.12	0.2639
0	4 (inferior-tubular)	5 (superior-tubular)	0.46	0.6449
0.16	1 (inferior-anterior)	2 (superior-anterior)	-0.13	0.8947
0.16	1 (inferior-anterior)	3 (posterior)	-1.20	0.2287
0.16	1 (inferior-anterior)	4 (inferior-tubular)	0.14	0.8910
0.16	1 (inferior-anterior)	5 (superior-tubular)	-1.20	0.2305
0.16	2 (superior-anterior)	3 (posterior)	-1.07	0.2839
0.16	2 (superior-anterior)	4 (inferior-tubular)	0.27	0.7877
0.16	2 (superior-anterior)	5 (superior-tubular)	-1.07	0.2860
0.16	3 (posterior)	4 (inferior-tubular)	1.34	0.1801
0.16	3 (posterior)	5 (superior-tubular)	0.00	0.9964
0.16	4 (inferior-tubular)	5 (superior-tubular)	-1.34	0.1816
37	1 (inferior-anterior)	2 (superior-anterior)	-0.29	0.7715
37	1 (inferior-anterior)	3 (posterior)	-1.25	0.2105
37	1 (inferior-anterior)	4 (inferior-tubular)	0.05	0.9621
37	1 (inferior-anterior)	5 (superior-tubular)	-0.64	0.5225
37	2 (superior-anterior)	3 (posterior)	-0.96	0.3366
37	2 (superior-anterior)	4 (inferior-tubular)	0.34	0.7346
37	2 (superior-anterior)	5 (superior-tubular)	-0.35	0.7279
37	3 (posterior)	4 (inferior-tubular)	1.31	0.1919
37	3 (posterior)	5 (superior-tubular)	0.62	0.5382
37	4 (inferior-tubular)	5 (superior-tubular)	-0.69	0.4904
92	1 (inferior-anterior)	2 (superior-anterior)	1.01	0.3107
92	1 (inferior-anterior)	3 (posterior)	-1.24	0.2161

Illuminance	subpart	vs. subpart	t-value	p-value
92	1 (inferior-anterior)	4 (inferior-tubular)	1.34	0.1801
92	1 (inferior-anterior)	5 (superior-tubular)	0.17	0.8668
92	2 (superior-anterior)	3 (posterior)	-2.25	**0.0246**
92	2 (superior-anterior)	4 (inferior-tubular)	0.33	0.7438
92	2 (superior-anterior)	5 (superior-tubular)	-0.85	0.3975
92	3 (posterior)	4 (inferior-tubular)	2.58	**0.0101**
92	3 (posterior)	5 (superior-tubular)	1.41	0.1602
92	4 (inferior-tubular)	5 (superior-tubular)	-1.17	0.2409
190	1 (inferior-anterior)	2 (superior-anterior)	-0.56	0.5782
190	1 (inferior-anterior)	3 (posterior)	-2.80	**0.0053**
190	1 (inferior-anterior)	4 (inferior-tubular)	0.35	0.7229
190	1 (inferior-anterior)	5 (superior-tubular)	-1.45	0.1479
190	2 (superior-anterior)	3 (posterior)	-2.24	**0.0254**
190	2 (superior-anterior)	4 (inferior-tubular)	0.91	0.3626
190	2 (superior-anterior)	5 (superior-tubular)	-0.89	0.3727
190	3 (posterior)	4 (inferior-tubular)	3.15	**0.0017**
190	3 (posterior)	5 (superior-tubular)	1.35	0.1781
190	4 (inferior-tubular)	5 (superior-tubular)	-1.80	0.0718

Supplementary Table 6-6. Post hoc contrasts between hypothalamus subpart for each illuminance during the emotional task.

Illuminance	subpart	vs. subpart	t-value	p-value
0	1 (inferior-anterior)	2 (superior-anterior)	0.45	0.6504
0	1 (inferior-anterior)	3 (posterior)	0.56	0.5775
0	1 (inferior-anterior)	4 (inferior-tubular)	-0.34	0.7355
0	1 (inferior-anterior)	5 (superior-tubular)	-1.50	0.1349
0	2 (superior-anterior)	3 (posterior)	0.10	0.9173
0	2 (superior-anterior)	4 (inferior-tubular)	-0.79	0.4289
0	2 (superior-anterior)	5 (superior-tubular)	-1.95	0.0515
0	3 (posterior)	4 (inferior-tubular)	-0.90	0.3709
0	3 (posterior)	5 (superior-tubular)	-2.05	**0.0403**
0	4 (inferior-tubular)	5 (superior-tubular)	-1.16	0.2470
0.16	1 (inferior-anterior)	2 (superior-anterior)	1.38	0.1684
0.16	1 (inferior-anterior)	3 (posterior)	0.52	0.6049
0.16	1 (inferior-anterior)	4 (inferior-tubular)	0.76	0.4455
0.16	1 (inferior-anterior)	5 (superior-tubular)	-0.42	0.6773
0.16	2 (superior-anterior)	3 (posterior)	-0.86	0.3896
0.16	2 (superior-anterior)	4 (inferior-tubular)	-0.62	0.5387
0.16	2 (superior-anterior)	5 (superior-tubular)	-1.79	0.0730
0.16	3 (posterior)	4 (inferior-tubular)	0.25	0.8059
0.16	3 (posterior)	5 (superior-tubular)	-0.93	0.3507
0.16	4 (inferior-tubular)	5 (superior-tubular)	-1.18	0.2385
37	1 (inferior-anterior)	2 (superior-anterior)	0.32	0.7454
37	1 (inferior-anterior)	3 (posterior)	-0.45	0.6497
37	1 (inferior-anterior)	4 (inferior-tubular)	-0.58	0.5602
37	1 (inferior-anterior)	5 (superior-tubular)	-1.01	0.3136
37	2 (superior-anterior)	3 (posterior)	-0.78	0.4361
37	2 (superior-anterior)	4 (inferior-tubular)	-0.91	0.3644
37	2 (superior-anterior)	5 (superior-tubular)	-1.33	0.1828
37	3 (posterior)	4 (inferior-tubular)	-0.13	0.8979
37	3 (posterior)	5 (superior-tubular)	-0.55	0.5798
37	4 (inferior-tubular)	5 (superior-tubular)	-0.43	0.6706
92	1 (inferior-anterior)	2 (superior-anterior)	1.19	0.2355
92	1 (inferior-anterior)	3 (posterior)	-1.35	0.1788

Illuminance	subpart	vs. subpart	t-value	p-value
92	1 (inferior-anterior)	4 (inferior-tubular)	0.11	0.9111
92	1 (inferior-anterior)	5 (superior-tubular)	-1.77	0.0772
92	2 (superior-anterior)	3 (posterior)	-2.53	**0.0115**
92	2 (superior-anterior)	4 (inferior-tubular)	-1.08	0.2825
92	2 (superior-anterior)	5 (superior-tubular)	-2.96	**0.0032**
92	3 (posterior)	4 (inferior-tubular)	1.46	0.1454
92	3 (posterior)	5 (superior-tubular)	-0.42	0.6721
92	4 (inferior-tubular)	5 (superior-tubular)	-1.88	0.0603
190	1 (inferior-anterior)	2 (superior-anterior)	1.54	0.1237
190	1 (inferior-anterior)	3 (posterior)	-3.31	**0.0010**
190	1 (inferior-anterior)	4 (inferior-tubular)	-0.18	0.8549
190	1 (inferior-anterior)	5 (superior-tubular)	-2.50	**0.0126**
190	2 (superior-anterior)	3 (posterior)	-4.85	**<.0001**
190	2 (superior-anterior)	4 (inferior-tubular)	-1.72	0.0851
190	2 (superior-anterior)	5 (superior-tubular)	-4.04	**<.0001**
190	3 (posterior)	4 (inferior-tubular)	3.13	**0.0018**
190	3 (posterior)	5 (superior-tubular)	0.81	0.4182
190	4 (inferior-tubular)	5 (superior-tubular)	-2.32	**0.0208**

Supplementary Table 6-7. Association between performance to the 2-back task and the activity of each hypothalamus subpart during each illuminance.

	F-value	p-value	Partial R^2
1 (inferior-anterior hypothalamus subpart)			
Subpart activity	< 0.01	0.99	
Illuminance	1.94	0.13	
Age	0.04	0.84	
Sex	6.43	**0.019**	0.23
BMI	2.02	0.16	
2 (superior-anterior hypothalamus subpart)			
Subpart activity	0.62	0.43	
Illuminance	2.24	0.07	
Age	0.01	0.94	
Sex	6.36	**0.019**	0.22
BMI	2.04	0.17	
3 (Posterior hypothalamus subpart)			
Subpart activity	9.43	**0.0027**	0.08
Illuminance	2.72	**0.034**	0.1
Age	0.04	0.85	
Sex	6.07	**0.022**	0.21
BMI	1.82	0.19	
4 (inferior-tubular hypothalamus subpart)			
Subpart activity	0.12	0.7	
Illuminance	2.09	0.11	
Age	0.03	0.86	
Sex	6.54	**0.018**	0.23
BMI	2.01	0.17	
5 (superior-tubular hypothalamus subpart)			
Subpart activity	0.25	0.62	
Illuminance	2.12	0.084	
Age	0.02	0.88	
Sex	6.1	**0.021**	0.21
BMI	2.01	0.17	

Appendix 3.

Supplementary Tables for Exposure to light modulates the activity of the human medial amygdala during emotional processing.

Supplementary Table 6-8. Data of participants included in the current analyses.

	Mean (SD)
Number of Participants	29
Age	24y ±3.1
Sex (M)	11
Mood (BDI-II)	7.9±7.0
Anxiety (BAI)	5.1±4.2
Sleep quality (PSQI)	4.1±2.6
Seasonality (SPAQ)	1.2±0.9
Chronotype (HO)	48.3±7.6
Daytime sleepiness (ESS)	6.2±2.9
Years of Education	14.2±3.1
Sleep duration (night before fMRI protocol)	7.9±0.7

Total number of participants who completed the study. BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; PSQI, Pittsburgh Sleep Quality Index; SPAQ, Seasonal Pattern Assessment Questionnaire; HO, Horne and Östberg; ESS, Epworth Sleepiness Scale. Refer to the method for the references.

Supplementary Table 6-9. Table of light characteristics.

	Low BEL	Mid BEL	High BEL	Monochromatic light (589nm)
Lux	47	116	240	7.5
Peak Spectral Irradiance (nm)	460	460	460	590
Melanopic EDI (lux ; ipRGCs)	37	92	190	0.16
Rhodopic EDI (lux ; Rods)	39	97	201	0.94
Cyanopic EDI (lux ; S-cones)	32	79	163	0
Chloropic EDI (lux; M-cones)	44	110	227	5
Erythropic EDI (lux ; L-cones)	46	113	233	8
Irradiance (μW/cm²)	15	36	75	1.4
Photon flux(1/cm²/s)	4.12^{E}+13	1.02^{E}+14	2.10^{E}+14	4.24^{E}+12
Log Photon Flux (log_{10} (1/cm²/s)	13.61	14.01	14.32	12.63
Narrowband peak	-	-	-	589
Narrowband FWHM	-	-	-	10

Detailed light characteristics of the four light conditions used in fMRI protocol. Blue enriched light (BEL) (low, mid, and high) and monochromatic light (589nm).

Supplementary Table 6-10. Post hoc contrasts between illuminances within each amygdala subpart.

Pairwise comparisons			
Amygdala subpart	**Contrast[#]**	**t-value**	**P_{-value}**
1	0 vs 0.16	0.15	0.99
1	0 vs 37	0.74	0.94
1	0 vs 92	1.04	0.83
1	0 vs 190	1.39	0.63
1	0.16 vs 37	0.59	0.97
1	0.16 vs 92	0.89	0.90
1	0.16 vs 190	1.24	0.73
1	37 vs 92	0.29	0.99
1	37 vs 190	0.64	0.96
1	92 vs 190	0.35	0.99
2	0 vs 0.16	-0.65	0.96
2	0 vs 37	0.45	0.99
2	0 vs 92	0.77	0.93
2	0 vs 190	1.2	0.74
2	0.16 vs 37	1.1	0.80
2	0.16 vs 92	1.42	0.61
2	0.16 vs 190	1.85	0.34
2	37 vs 92	0.31	0.99
2	37 vs 190	0.74	0.94
2	92 vs 190	0.43	0.99
3	0 vs 0.16	-0.73	0.95
3	0 vs 37	1.09	0.80
3	0 vs 92	-0.09	1
3	0 vs 190	3.42	**0.005**
3	0.16 vs 37	1.82	0.36
3	0.16 vs 92	0.64	0.96
3	0.16 vs 190	4.15	**0.0003**
3	37 vs 92	-1.18	0.76
3	37 vs 190	2.31	0.14
3	92 vs 190	3.51	**0.004**
4	0 vs 0.16	-0.71	0.95
4	0 vs 37	-0.61	0.97
4	0 vs 92	-0.99	0.86
4	0 vs 190	-0.54	0.98
4	0.16 vs 37	0.1	1
4	0.16 vs 92	-0.28	0.99
4	0.16 vs 190	0.16	0.99
4	37 vs 92	-0.38	0.99
4	37 vs 190	0.06	1
4	92 vs 190	0.43	0.99
5	0 vs 0.16	-0.09	1
5	0 vs 37	0.85	0.91
5	0 vs 92	0.46	0.99
5	0 vs 190	3.8	**0.001**
5	0.16 vs 37	0.94	0.88
5	0.16 vs 92	0.55	0.98
5	0.16 vs 190	3.89	**0.001**
5	37 vs 92	-0.38	0.99
5	37 vs 190	2.95	**0.02**
5	92 vs 190	3.3	**0.008**

6	0 vs 0.16	0.15	0.99
6	0 vs 37	0.22	0.99
6	0 vs 92	-0.32	0.99
6	0 vs 190	0.97	0.87
6	0.16 vs 37	0.07	1
6	0.16 vs 92	-0.47	0.99
6	0.16 vs 190	0.82	0.92
6	37 vs 92	-0.54	0.98
6	37 vs 190	0.73	0.94
6	92 vs 190	1.28	0.70
7	0 vs 0.16	0.39	0.99
7	0 vs 37	1.14	0.78
7	0 vs 92	0.67	0.96
7	0 vs 190	3.18	**0.01**
7	0.16 vs 37	0.75	0.94
7	0.16 vs 92	0.27	0.99
7	0.16 vs 190	2.79	**0.04**
7	37 vs 92	-0.47	0.98
7	37 vs 190	2.02	0.25
7	92 vs 190	2.51	0.08
8	0 vs 0.16	-0.21	0.99
8	0 vs 37	0.08	1
8	0 vs 92	-0.27	0.99
8	0 vs 190	-1.09	0.81
8	0.16 vs 37	0.28	0.99
8	0.16 vs 92	-0.07	1
8	0.16 vs 190	-0.89	0.90
8	37 vs 92	-0.35	0.99
8	37 vs 190	-1.18	0.76
8	92 vs 190	-0.82	0.92
9	0 vs 0.16	0.31	0.99
9	0 vs 37	-0.05	1
9	0 vs 92	0.63	0.97
9	0 vs 190	4.46	**<.0001**
9	0.16 vs 37	-0.35	0.99
9	0.16 vs 92	0.31	0.99
9	0.16 vs 190	4.09	**0.0004**
9	37 vs 92	0.67	0.96
9	37 vs 190	4.5	**<.0001**
9	92 vs 190	3.8	**0.001**
10	0 vs 0.16	-0.43	0.99
10	0 vs 37	0.19	0.99
10	0 vs 92	0.12	1
10	0 vs 190	0.18	0.99
10	0.16 vs 37	0.62	0.97
10	0.16 vs 92	0.55	0.98
10	0.16 vs 190	0.61	0.97
10	37 vs 92	-0.08	1
10	37 vs 190	-0.01	1
10	92 vs 190	0.07	1

Supplementary Table 6-11. Post hoc contrasts between amygdala subparts for each illuminance.

Pairwise comparisons			
Illuminance	**Contrast[#]**	**t-value**	**P_{-value}**
0	**1 vs 2**	0.85	1.00
0	**1 vs 3**	-1.07	0.99
0	**1 vs 4**	0.7	1.00
0	**1 vs 5**	-1.43	0.92
0	**1 vs 6**	0.31	1.00
0	**1 vs 7**	-1.37	0.94
0	**1 vs 8**	0.13	1.00
0	**1 vs 9**	-1.3	0.95
0	**1 vs 10**	0.22	1.00
0	**2 vs 3**	-1.92	0.65
0	**2 vs 4**	-0.14	1.00
0	**2 vs 5**	-2.28	0.40
0	**2 vs 6**	-0.54	1.00
0	**2 vs 7**	-2.21	0.45
0	**2 vs 8**	-0.72	1.00
0	**2 vs 9**	-2.15	0.49
0	**2 vs 10**	-0.64	1.00
0	**3 vs 4**	1.76	0.76
0	**3 vs 5**	-0.35	1.00
0	**3 vs 6**	1.38	0.93
0	**3 vs 7**	-0.31	1.00
0	**3 vs 8**	1.19	0.97
0	**3 vs 9**	-0.23	1.00
0	**3 vs 10**	1.29	0.96
0	**4 vs 5**	-2.11	0.52
0	**4 vs 6**	-0.39	1.00
0	**4 vs 7**	-2.05	0.56

0	**4 vs 8**	-0.57	1.00
0	**4 vs 9**	-1.99	0.60
0	**4 vs 10**	-0.49	1.00
0	**5 vs 6**	1.73	0.78
0	**5 vs 7**	0.04	1.00
0	**5 vs 8**	1.55	0.87
0	**5 vs 9**	0.12	1.00
0	**5 vs 10**	1.64	0.83
0	**6 vs 7**	-1.68	0.81
0	**6 vs 8**	-0.18	1.00
0	**6 vs 9**	-1.61	0.84
0	**6 vs 10**	-0.09	1.00
0	**7 vs 8**	1.49	0.90
0	**7 vs 9**	0.09	1.00
0	**7 vs 10**	1.59	0.86
0	**8 vs 9**	-1.42	0.92
0	**8 vs 10**	0.09	1.00
0	**9 vs 10**	1.52	0.89
0.16	**1 vs 2**	0.14	1.00
0.16	**1 vs 3**	-1.85	0.70
0.16	**1 vs 4**	-0.06	1.00
0.16	**1 vs 5**	-1.64	0.83
0.16	**1 vs 6**	0.31	1.00
0.16	**1 vs 7**	-1.15	0.98
0.16	**1 vs 8**	-0.19	1.00
0.16	**1 vs 9**	-1.15	0.98
0.16	**1 vs 10**	-0.3	1.00
0.16	**2 vs 3**	-1.99	0.60
0.16	**2 vs 4**	-0.2	1.00
0.16	**2 vs 5**	-1.78	0.75

0.16	**2 vs 6**	0.17	1.00
0.16	**2 vs 7**	-1.29	0.96
0.16	**2 vs 8**	-0.33	1.00
0.16	**2 vs 9**	-1.29	0.96
0.16	**2 vs 10**	-0.44	1.00
0.16	**3 vs 4**	1.78	0.75
0.16	**3 vs 5**	0.21	1.00
0.16	**3 vs 6**	2.16	0.49
0.16	**3 vs 7**	0.68	1.00
0.16	**3 vs 8**	1.65	0.82
0.16	**3 vs 9**	0.68	1.00
0.16	**3 vs 10**	1.55	0.87
0.16	**4 vs 5**	-1.57	0.86
0.16	**4 vs 6**	0.37	1.00
0.16	**4 vs 7**	-1.08	0.99
0.16	**4 vs 8**	-0.13	1.00
0.16	**4 vs 9**	-1.08	0.99
0.16	**4 vs 10**	-0.24	1.00
0.16	**5 vs 6**	1.95	0.64
0.16	**5 vs 7**	0.47	1.00
0.16	**5 vs 8**	1.44	0.92
0.16	**5 vs 9**	0.47	1.00
0.16	**5 vs 10**	1.34	0.95
0.16	**6 vs 7**	-1.45	0.91
0.16	**6 vs 8**	-0.5	1.00
0.16	**6 vs 9**	-1.45	0.91
0.16	**6 vs 10**	-0.61	1.00
0.16	**7 vs 8**	0.96	0.99
0.16	**7 vs 9**	0	1.00
0.16	**7 vs 10**	0.85	1.00

0.16	**8 vs 9**	-0.95	0.99
0.16	**8 vs 10**	-0.11	1.00
0.16	**9 vs 10**	0.85	1.00
37	**1 vs 2**	0.59	1.00
37	**1 vs 3**	-0.76	1.00
37	**1 vs 4**	-0.5	1.00
37	**1 vs 5**	-1.33	0.95
37	**1 vs 6**	-0.15	1.00
37	**1 vs 7**	-0.99	0.99
37	**1 vs 8**	-0.47	1.00
37	**1 vs 9**	-2	0.60
37	**1 vs 10**	-0.27	1.00
37	**2 vs 3**	-1.34	0.94
37	**2 vs 4**	-1.08	0.99
37	**2 vs 5**	-1.92	0.66
37	**2 vs 6**	-0.74	1.00
37	**2 vs 7**	-1.57	0.86
37	**2 vs 8**	-1.06	0.99
37	**2 vs 9**	-2.58	0.23
37	**2 vs 10**	-0.87	1.00
37	**3 vs 4**	0.26	1.00
37	**3 vs 5**	-0.57	1.00
37	**3 vs 6**	0.6	1.00
37	**3 vs 7**	-0.24	1.00
37	**3 vs 8**	0.29	1.00
37	**3 vs 9**	-1.24	0.97
37	**3 vs 10**	0.48	1.00
37	**4 vs 5**	-0.83	1.00
37	**4 vs 6**	0.34	1.00
37	**4 vs 7**	-0.5	1.00

37	**4 vs 8**	0.03	1.00
37	**4 vs 9**	-1.5	0.89
37	**4 vs 10**	0.22	1.00
37	**5 vs 6**	1.17	0.98
37	**5 vs 7**	0.32	1.00
37	**5 vs 8**	0.87	1.00
37	**5 vs 9**	-0.67	1.00
37	**5 vs 10**	1.06	0.99
37	**6 vs 7**	-0.84	1.00
37	**6 vs 8**	-0.31	1.00
37	**6 vs 9**	-1.84	0.71
37	**6 vs 10**	-0.12	1.00
37	**7 vs 8**	0.53	1.00
37	**7 vs 9**	-0.98	0.99
37	**7 vs 10**	0.72	1.00
37	**8 vs 9**	-1.54	0.88
37	**8 vs 10**	0.19	1.00
37	**9 vs 10**	1.73	0.78
92	**1 vs 2**	0.62	1.00
92	**1 vs 3**	-2.07	0.55
92	**1 vs 4**	-1.1	0.99
92	**1 vs 5**	-1.92	0.66
92	**1 vs 6**	-0.89	1.00
92	**1 vs 7**	-1.68	0.81
92	**1 vs 8**	-1.03	0.99
92	**1 vs 9**	-1.65	0.82
92	**1 vs 10**	-0.6	1.00
92	**2 vs 3**	-2.69	0.18
92	**2 vs 4**	-1.71	0.79
92	**2 vs 5**	-2.53	0.25

92	**2 vs 6**	-1.51	0.89
92	**2 vs 7**	-2.29	0.40
92	**2 vs 8**	-1.65	0.82
92	**2 vs 9**	-2.26	0.42
92	**2 vs 10**	-1.22	0.97
92	**3 vs 4**	0.97	0.99
92	**3 vs 5**	0.14	1.00
92	**3 vs 6**	1.18	0.98
92	**3 vs 7**	0.37	1.00
92	**3 vs 8**	1.03	0.99
92	**3 vs 9**	0.41	1.00
92	**3 vs 10**	1.47	0.90
92	**4 vs 5**	-0.83	1.00
92	**4 vs 6**	0.21	1.00
92	**4 vs 7**	-0.59	1.00
92	**4 vs 8**	0.06	1.00
92	**4 vs 9**	-0.56	1.00
92	**4 vs 10**	0.5	1.00
92	**5 vs 6**	1.03	0.99
92	**5 vs 7**	0.23	1.00
92	**5 vs 8**	0.89	1.00
92	**5 vs 9**	0.27	1.00
92	**5 vs 10**	1.32	0.95
92	**6 vs 7**	-0.8	1.00
92	**6 vs 8**	-0.15	1.00
92	**6 vs 9**	-0.76	1.00
92	**6 vs 10**	0.29	1.00
92	**7 vs 8**	0.65	1.00
92	**7 vs 9**	0.04	1.00
92	**7 vs 10**	1.09	0.99

92	**8 vs 9**	-0.62	1.00
92	**8 vs 10**	0.44	1.00
92	**9 vs 10**	1.05	0.99
190	**1 vs 2**	0.69	1.00
190	**1 vs 3**	0.73	1.00
190	**1 vs 4**	-1.01	0.99
190	**1 vs 5**	0.71	1.00
190	**1 vs 6**	-0.07	1.00
190	**1 vs 7**	0.24	1.00
190	**1 vs 8**	-2.07	0.55
190	**1 vs 9**	1.44	0.91
190	**1 vs 10**	-0.85	1.00
190	**2 vs 3**	0.04	1.00
190	**2 vs 4**	-1.69	0.80
190	**2 vs 5**	0.02	1.00
190	**2 vs 6**	-0.75	1.00
190	**2 vs 7**	-0.44	1.00
190	**2 vs 8**	-2.76	0.15
190	**2 vs 9**	0.76	1.00
190	**2 vs 10**	-1.53	0.88
190	**3 vs 4**	-1.73	0.78
190	**3 vs 5**	-0.02	1.00
190	**3 vs 6**	-0.79	1.00
190	**3 vs 7**	-0.48	1.00
190	**3 vs 8**	-2.8	0.14
190	**3 vs 9**	0.72	1.00
190	**3 vs 10**	-1.58	0.86
190	**4 vs 5**	1.71	0.79
190	**4 vs 6**	0.94	1.00
190	**4 vs 7**	1.25	0.96

190	**4 vs 8**	-1.05	0.99
190	**4 vs 9**	2.42	0.31
190	**4 vs 10**	0.16	1.00
190	**5 vs 6**	-0.78	1.00
190	**5 vs 7**	-0.47	1.00
190	**5 vs 8**	-2.78	0.14
190	**5 vs 9**	0.74	1.00
190	**5 vs 10**	-1.56	0.87
190	**6 vs 7**	0.31	1.00
190	**6 vs 8**	-2.01	0.59
190	**6 vs 9**	1.51	0.89
190	**6 vs 10**	-0.78	1.00
190	**7 vs 8**	-2.32	0.38
190	**7 vs 9**	1.2	0.97
190	**7 vs 10**	-1.09	0.99
190	**8 vs 9**	3.5	**0.02**
190	**8 vs 10**	1.22	0.97
190	**9 vs 10**	-2.28	0.40

Supplementary Table 6-12. Post hoc contrasts between task stimuli for each illuminance.

Pairwise comparisons			
Illuminance	**Contrast#**	**t-value**	**P-value**
0	Neutral vs Emotional	-3.16	**0.001**
0.16	Neutral vs Emotional	-4.23	**<.0001**
37	Neutral vs Emotional	-4.35	**<.0001**
92	Neutral vs Emotional	-0.55	0.58
190	Neutral vs Emotional	-0.5	0.61

Supplementary Table 6-13. Post hoc contrasts between each illuminance for task stimuli.

Pairwise comparisons			
Task stimuli	**Contrast#**	**t-value**	**P-value**
Neutral	0 vs 0.16	0.21	0.99
Neutral	0 vs 37	1.61	0.49
Neutral	0 vs 92	-1.02	0.84
Neutral	0 vs 190	2.29	0.14
Neutral	0.16 vs 37	1.4	0.62
Neutral	0.16 vs 92	-1.22	0.73
Neutral	0.16 vs 190	2.08	0.23
Neutral	37 vs 92	-2.62	0.06
Neutral	37 vs 190	0.68	0.96
Neutral	92 vs 190	3.3	**0.008**
Emotional	0 vs 0.16	-1.01	0.85
Emotional	0 vs 37	0.24	0.99
Emotional	0 vs 92	1.92	0.30
Emotional	0 vs 190	5.28	**<.0001**
Emotional	0.16 vs 37	1.25	0.72
Emotional	0.16 vs 92	2.93	**0.02**
Emotional	0.16 vs 190	6.29	**<.0001**
Emotional	37 vs 92	1.67	0.45
Emotional	37 vs 190	5.03	**<.0001**
Emotional	92 vs 190	3.36	**0.007**

References

References

Adamantidis, A. R., Gutierrez Herrera, C., & Gent, T. C. (2019). Oscillating circuitries in the sleeping brain. In *Nature Reviews Neuroscience* (Vol. 20, Issue 12, pp. 746–762). Nature Publishing Group. https://doi.org/10.1038/s41583-019-0223-4

Adamantidis, A. R., Zhang, F., Aravanis, A. M., Deisseroth, K., & De Lecea, L. (2007). Neural substrates of awakening probed with optogenetic control of hypocretin neurons. *Nature 2007 450:7168*, *450*(7168), 420–424. https://doi.org/10.1038/nature06310

Adidharma, W., Leach, G., & Yan, L. (2012). Orexinergic signaling mediates light-induced neuronal activation in the dorsal raphe nucleus. *Neuroscience*, *220*, 201–207. https://doi.org/10.1016/J.NEUROSCIENCE.2012.06.020

Albers, H. E., Walton, J. C., Gamble, K. L., McNeill, J. K., & Hummer, D. L. (2017). The dynamics of GABA signaling: Revelations from the circadian pacemaker in the suprachiasmatic nucleus. *Frontiers in Neuroendocrinology*, *44*, 35–82. https://doi.org/10.1016/J.YFRNE.2016.11.003

Alkozei, A., Smith, R., Pisner, D. A., Vanuk, J. R., Markowski, S. M., Fridman, A., Shane, B. R., Knight, S. A., & Killgore, W. D. S. (2016). Exposure to Blue Light Increases Subsequent Functional Activation of the Prefrontal Cortex During Performance of a Working Memory Task. *Sleep*.

Allen, A. E., Martial, F. P., & Lucas, R. J. (2019). Form vision from melanopsin in humans. *Nature Communications*, *10*(1), 1–10. https://doi.org/10.1038/s41467-019-10113-3

Altimus, C. M., Güler, A. D., Alam, N. M., Arman, A. C., Prusky, G. T., Sampath, A. P., & Hattar, S. (2010). Rod photoreceptors drive circadian photoentrainment across a wide range of light intensities. *Nature Neuroscience 2010 13:9*, *13*(9), 1107–1112. https://doi.org/10.1038/nn.2617

Altimus, C. M., Güler, A. D., Villa, K. L., McNeill, D. S., LeGates, T. A., & Hattar, S. (2008). Rods-cones and melanopsin detect light and dark to modulate sleep independent of image formation. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(50), 19998–20003. https://doi.org/10.1073/pnas.0808312105

An, K., Zhao, H., Miao, Y., Xu, Q., Li, Y. F., Ma, Y. Q., Shi, Y. M., Shen, J. W., Meng, J. J., Yao, Y. G., Zhang, Z., Chen, J. T., Bao, J., Zhang, M., & Xue, T. (2020). A circadian rhythm-gated subcortical pathway for nighttime-light-induced depressive-like behaviors in mice. *Nature Neuroscience*, *23*(7), 869–880. https://doi.org/10.1038/s41593-020-0640-8

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, *26*(3), 839–851. https://doi.org/10.1016/J.NEUROIMAGE.2005.02.018

Aston-Jones, G., Chen, S., Zhu, Y., & Oshinsky, M. L. (2001). A neural circuit for circadian regulation of arousal. *Nature Neuroscience*, *4*(7), 732–738. https://doi.org/10.1038/89522

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annual Review of Neuroscience*, *28*, 403–450. https://doi.org/10.1146/ANNUREV.NEURO.28.061604.135709

Aston-Jones, G., Foote, S. L., & Segal, M. (1985). Impulse conduction properties of noradrenergic locus coeruleus axons projecting to monkey cerebrocortex. *Neuroscience*, *15*(3). https://doi.org/10.1016/0306-4522(85)90077-6

Baas, D., Aleman, A., & Kahn, R. S. (2004). Lateralization of amygdala activation: A systematic review of functional neuroimaging studies. *Brain Research Reviews*, *45*(2), 96–103. https://doi.org/10.1016/j.brainresrev.2004.02.004

Bano-Otalora, B., Martial, F., Harding, C., Bechtold, D. A., Allen, A. E., Brown, T. M., Belle, M. D. C., & Lucas, R. J. (2021). Bright daytime light enhances circadian amplitude in a diurnal mammal. *Proceedings of the National Academy of Sciences of the United States of America*, *118*(22), e2100094118. https://doi.org/10.1073/PNAS.2100094118/SUPPL_FILE/PNAS.2100094118.SAPP.PDF

Banse, R., & Scherer, K. R. (1996). Acoustic profiles in vocal emotion expression. *Journal of Personality and Social Psychology*, *70*(3), 614–636. https://doi.org/10.1037//0022-3514.70.3.614

Barbini, B., Di Molfetta, D., Gasperini, M., Manfredonia, M. G., & Smeraldi, E. (1995). Seasonal concordance of recurrence in mood disorder patients. *European Psychiatry*, *10*(4), 171–174. https://doi.org/10.1016/0767-399X(96)80060-5

Bartels, A., & Zeki, S. (2000). The neural basis of romantic love. *Neuroreport*, *11*(17), 3829–3834. https://doi.org/10.1097/00001756-200011270-00046

Beatty, J. (1982). Task-evoked pupillary responses, processing load, and the structure of processing resources. *Psychological Bulletin*, *91*(2), 276–292. https://doi.org/10.1037/0033-2909.91.2.276

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*(6), 893–897. https://doi.org/10.1037/0022-006X.56.6.893

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, *8*(1), 77–100. https://doi.org/10.1016/0272-7358(88)90050-5

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*(6), 561–571. https://doi.org/10.1001/ARCHPSYC.1961.01710120031004

Beckers, E., Campbell, I., Sharifpour, R., Paparella, I., Berger, A., Aizpurua, J. F. B., Koshmanova, E., Mortazavi, N., Talwar, P., Sherif, S., Jacobs, H. I. L., & Vandewalle, G. (2023). Impact of repeated short light exposures on sustained pupil responses in an fMRI environment. *Journal of Sleep Research*, e14085. https://doi.org/10.1111/JSR.14085

Bedrosian, T. A., Weil, Z. M., & Nelson, R. J. (2013). Chronic dim light at night provokes reversible depression-like phenotype: possible role for TNF. *Molecular Psychiatry*, *18*(8), 930–936. https://doi.org/10.1038/mp.2012.96

Behar-Cohen, F., Martinsons, C., Viénot, F., Zissis, G., Barlier-Salsi, A., Cesarini, J. P., Enouf, O., Garcia, M., Picaud, S., & Attia, D. (2011). Light-emitting diodes (LED) for domestic lighting: Any

risks for the eye? *Progress in Retinal and Eye Research*, *30*(4), 239–257. https://doi.org/10.1016/J.PRETEYERES.2011.04.002

Benedetti, M., Maierová, L., Cajochen, C., Scartezzini, J. L., & Münch, M. (2022). Optimized office lighting advances melatonin phase and peripheral heat loss prior bedtime. *Scientific Reports 2022 12:1*, *12*(1), 1–13. https://doi.org/10.1038/s41598-022-07522-8

Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, *42*(1), 33–84. https://doi.org/10.1016/S0165-0173(03)00143-7

Berson, D. M., Dunn, F. A., & Takao, M. (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science*, *295*(5557), 1070–1073. https://doi.org/10.1126/science.1067262

Billot, B., Bocchetta, M., Todd, E., Dalca, A. V., Rohrer, J. D., & Iglesias, J. E. (2020). Automated segmentation of the hypothalamus and associated subunits in brain MRI. *NeuroImage*, *223*, 117287. https://doi.org/10.1016/J.NEUROIMAGE.2020.117287

Blume, C., Cajochen, C., Schöllhorn, I., Slawik, H. C., & Spitschan, M. (2023). Effects of calibrated blue–yellow changes in light on the human circadian clock. *Nature Human Behaviour 2023*, 1–16. https://doi.org/10.1038/s41562-023-01791-7

Boyce, P. R. (2022). Light, lighting and human health. *Lighting Research and Technology*, *54*(2), 101–144. https://doi.org/10.1177/14771535211010267/ASSET/IMAGES/10.1177_14771535211010267-IMG1.PNG

Braak, H., & Del Tredici, K. (2015). The preclinical phase of the pathological process underlying sporadic Alzheimer's disease. *Brain : A Journal of Neurology*, *138*(Pt 10), 2814–2833. https://doi.org/10.1093/BRAIN/AWV236

Bradley, M. M., Miccoli, L., Escrig, M. A., & Lang, P. J. (2008). The pupil as a measure of emotional arousal and autonomic activation. *Psychophysiology*, *45*(4), 602–607. https://doi.org/10.1111/J.1469-8986.2008.00654.X

Brainard, G. C., Hanifin, J. R., Greeson, J. M., Byrne, B., Glickman, G., Gerner, E., & Rollag, M. D. (2001). Action spectrum for melatonin regulation in humans: Evidence for a novel circadian photoreceptor. *Journal of Neuroscience*, *21*(16), 6405–6412. https://doi.org/10.1523/jneurosci.21-16-06405.2001

Brown, T. M. (2020). Melanopic illuminance defines the magnitude of human circadian light responses under a wide range of conditions. *Journal of Pineal Research*, *69*(1). https://doi.org/10.1111/JPI.12655

Brown, T. M., Brainard, G. C., Cajochen, C., Czeisler, C. A., Hanifin, J. P., Lockley, S. W., Lucas, R. J., Münch, M., O'Hagan, J. B., Peirson, S. N., Price, L. L. A., Roenneberg, T., Schlangen, L. J. M., Skene, D. J., Spitschan, M., Vetter, C., Zee, P. C., & Wright, K. P. (2022). Recommendations for daytime, evening, and nighttime indoor light exposure to best support physiology, sleep, and wakefulness in healthy adults. *PLoS Biology*, *20*(3), e3001571. https://doi.org/10.1371/JOURNAL.PBIO.3001571

Brown, T. M., Gias, C., Hatori, M., Keding, S. R., Semo, M., Coffey, P. J., Gigg, J., Piggins, H. D., Panda, S., & Lucas, R. J. (2010). Melanopsin Contributions to Irradiance Coding in the Thalamo-Cortical Visual System. *PLoS Biology*, *8*(12), e1000558. https://doi.org/10.1371/journal.pbio.1000558

Brown, T. M., Thapan, K., Arendt, J., Revell, V. L., & Skene, D. J. (2021). S-cone contribution to the acute melatonin suppression response in humans. *Journal of Pineal Research*, *71*(1). https://doi.org/10.1111/JPI.12719

Brown, T. M., Tsujimura, S. I., Allen, A. E., Wynne, J., Bedford, R., Vickery, G., Vugler, A., & Lucas, R. J. (2012). Melanopsin-based brightness discrimination in mice and humans. *Current Biology*, *22*(12), 1134–1141. https://doi.org/10.1016/j.cub.2012.04.039

Bullough, J. D., Bierman, A., & Rea, M. S. (2017). Evaluating the blue-light hazard from solid state lighting. *Https://Doi.Org/10.1080/10803548.2017.1375172*, *25*(2), 311–320. https://doi.org/10.1080/10803548.2017.1375172

Buysse, D. J., Reynolds, C. F. 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

Cajochen, C., Frey, S., Anders, D., Späti, J., Bues, M., Pross, A., Mager, R., Wirz-Justice, A., & Stefani, O. (2011). Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. *Journal of Applied Physiology*, *110*(5), 1432–1438. https://doi.org/10.1152/japplphysiol.00165.2011

Cajochen, C., Münch, M., Kobialka, S., Kräuchi, K., Steiner, R., Oelhafen, P., Orgül, S., & Wirz-Justice, A. (2005). High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. *Journal of Clinical Endocrinology and Metabolism*, *90*(3), 1311–1316. https://doi.org/10.1210/jc.2004-0957

Cajochen, C., Zeitzer, J. M., Czeisler, C. A., & Dijk, D. J. (2000). Dose-response relationship for light intensity and ocular and electroencephalographic correlates of human alertness. *Behavioural Brain Research*, *115*(1), 75–83. https://doi.org/10.1016/S0166-4328(00)00236-9

Campbell, I., Beckers, E., Sharifpour, R., Berger, A., Paparella, I., Aizpurua, J. F. B., Koshmanova, E., Mortazavi, N., Sherif, S., & Vandewalle, G. (2023). Impact of light on task-evoked pupil responses during cognitive tasks. *Journal of Sleep Research*, e14101. https://doi.org/10.1111/JSR.14101

Campbell, I., Sharifpour, R., Aizpurua, J. F. B., Beckers, E., Paparella, I., Berger, A., Koshmanova, E., Mortazavi, N., Read, J., Zubkov, M., Talwar, P., Collette, F., Sherif, S., Phillips, C., Lamalle, L., & Vandewalle, G. (2023). Regional response to light illuminance across the human hypothalamus. *BioRxiv*, 2023.12.19.572317. https://doi.org/10.1101/2023.12.19.572317

Campbell, I., Sharifpour, R., & Vandewalle, G. (2023). Light as a Modulator of Non-Image-Forming Brain Functions—Positive and Negative Impacts of Increasing Light Availability. *Clocks & Sleep*, *5*(1), 116. https://doi.org/10.3390/CLOCKSSLEEP5010012

Canazei, M., Weninger, J., Pohl, W., Marksteiner, J., & Weiss, E. M. (2022). Effects of dynamic bedroom lighting on measures of sleep and circadian rest-activity rhythm in inpatients with

major depressive disorder. *Scientific Reports 2022 12:1*, *12*(1), 1–12. https://doi.org/10.1038/s41598-022-10161-8

Chellappa, S. L. (2021). Individual differences in light sensitivity affect sleep and circadian rhythms. *Sleep*, *44*(2), 1–10. https://doi.org/10.1093/SLEEP/ZSAA214

Chellappa, S. L., Ly, J. Q. M., Meyer, C., Balteau, E., Degueldre, C., Luxen, A., Phillips, C., Cooper, H. M., & Vandewalle, G. (2014). Photic memory for executive brain responses. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(16), 6087–6091. https://doi.org/10.1073/pnas.1320005111

Chellappa, S. L., Steiner, R., Oelhafen, P., & Cajochen, C. (2017). Sex differences in light sensitivity impact on brightness perception, vigilant attention and sleep in humans. *Scientific Reports*, *7*(1), 14215. https://doi.org/10.1038/s41598-017-13973-1

Chellappa, S. L., Steiner, R., Oelhafen, P., Lang, D., Götz, T., Krebs, J., & Cajochen, C. (2013). Acute exposure to evening blue-enriched light impacts on human sleep. *Journal of Sleep Research*, *22*(5), 573–580. https://doi.org/10.1111/jsr.12050

Chen, Y., Chen, T., & Cai, X. (2021). Light-sensitive circuits related to emotional processing underlie the antidepressant neural targets of light therapy. *Behavioural Brain Research*, *396*. https://doi.org/10.1016/J.BBR.2020.112862

CIE Position Statement on the Blue Light Hazard. (2019). https://doi.org/10.1080/15502724.2016.1145551

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., & Smith, E. E. (1997). Temporal dynamics of brain activation during a working memory task. *Nature 1997 386:6625*, *386*(6625), 604–608. https://doi.org/10.1038/386604a0

Collette, F., Hogge, M., Salmon, E., & Van der Linden, M. (2006). Exploration of the neural substrates of executive functioning by functional neuroimaging. *Neuroscience*, *139*(1), 209–221. https://doi.org/10.1016/J.NEUROSCIENCE.2005.05.035

Collette, F., Van Der Linden, M., Laureys, S., Delfiore, G., Degueldre, C., Luxen, A., & Salmon, E. (2005). Exploring the unity and diversity of the neural substrates of executive functioning. *Human Brain Mapping*, *25*(4), 409–423. https://doi.org/10.1002/hbm.20118

Costa, V. D., & Rudebeck, P. H. (2016). More than Meets the Eye: The Relationship between Pupil Size and Locus Coeruleus Activity. *Neuron*, *89*(1), 8–10. https://doi.org/10.1016/J.NEURON.2015.12.031

Cremascoli, R., Sparasci, D., Giusti, G., Cattaldo, S., Prina, E., Roveta, F., Bruno, F., Ghezzi, C., Cerri, S., Picascia, M., Bernini, S., Sinforiani, E., Terzaghi, M., Priano, L., Mauro, A., & Manni, R. (2022). Effects of Circadian Phase Tailored Light Therapy on Sleep, Mood, and Cognition in Alzheimer's Disease: Preliminary Findings in a Pivotal Study. *Frontiers in Physiology*, *12*, 2205. https://doi.org/10.3389/FPHYS.2021.755322/BIBTEX

Czeisler, C. A., Duffy, J. F., Shanahan, T. L., Brown, E. N., Mitchell, J. F., Rimmer, D. W., Ronda, J. M., Silva, E. J., Allan, J. S., Emens, J. S., Dijk, D. J., & Kronauer, R. E. (1999). Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science (New York, N.Y.)*, *284*(5423), 2177–2181. https://doi.org/10.1126/SCIENCE.284.5423.2177

Czeisler, C. A., Shanahan, T. L., Klerman, E. B., Martens, H., Brotman, D. J., Emens, J. S., Klein, T., & Rizzo, J. F. (1995). Suppression of Melatonin Secretion in Some Blind Patients by Exposure to Bright Light. *New England Journal of Medicine*, *332*(1), 6–11. https://doi.org/10.1056/NEJM199501053320102

Daneault, V., Dumont, M., Massé, É., Forcier, P., Boré, A., Lina, J. M., Doyon, J., Vandewalle, G., & Carrier, J. (2018). Plasticity in the sensitivity to light in aging: Decreased non-visual impact of light on cognitive brain activity in older individuals but no impact of lens replacement. *Frontiers in Physiology*, *9*(NOV). https://doi.org/10.3389/fphys.2018.01557

Daneault, V., Dumont, M., Massé, Vandewalle, G., & Carrier, J. (2016). Light-sensitive brain pathways and aging. In *Journal of Physiological Anthropology*. https://doi.org/10.1186/s40101-016-0091-9

Daneault, V., Hébert, M., Albouy, G., Doyon, J., Dumont, M., Carrier, J., & Vandewalle, G. (2014). Aging reduces the stimulating effect of blue light on cognitive brain functions. *Sleep*, *37*(1), 85–96. https://doi.org/10.5665/sleep.3314

Davern, P. J., & Head, G. A. (2011). Role of the medial amygdala in mediating responses to aversive stimuli leading to hypertension. *Clinical and Experimental Pharmacology and Physiology*, *38*(2), 136–143. https://doi.org/10.1111/J.1440-1681.2010.05413.X

de Gee, J. W., Colizoli, O., Kloosterman, N. A., Knapen, T., Nieuwenhuis, S., & Donner, T. H. (2017). Dynamic modulation of decision biases by brainstem arousal systems. *ELife*, *6*. https://doi.org/10.7554/ELIFE.23232

De Lecea, L. (2015). Optogenetic Control of Hypocretin (Orexin) Neurons and Arousal Circuits. *Current Topics in Behavioral Neurosciences*, *25*, 367. https://doi.org/10.1007/7854_2014_364

Delwig, A., Larsen, D. D., Yasumura, D., Yang, C. F., Shah, N. M., & Copenhagen, D. R. (2016). Retinofugal Projections from Melanopsin-Expressing Retinal Ganglion Cells Revealed by Intraocular Injections of Cre-Dependent Virus. *PLOS ONE*, *11*(2), e0149501. https://doi.org/10.1371/JOURNAL.PONE.0149501

Didikoglu, A., Mohammadian, N., Johnson, S., van Tongeren, M., Wright, P., Casson, A. J., Brown, T. M., & Lucas, R. J. (2023). Associations between light exposure and sleep timing and sleepiness while awake in a sample of UK adults in everyday life. *Proceedings of the National Academy of Sciences of the United States of America*, *120*(42). https://doi.org/10.1073/PNAS.2301608120

Dijk, D. J., Duffy, J. F., Silva, E. J., Shanahan, T. L., Boivin, D. B., & Czeisler, C. A. (2012). Amplitude reduction and phase shifts of melatonin, cortisol and other circadian rhythms after a gradual advance of sleep and light exposure in humans. *PloS One*, *7*(2). https://doi.org/10.1371/JOURNAL.PONE.0030037

Do, A., Li, V. W., Huang, S., Michalak, E. E., Tam, E. M., Chakrabarty, T., Yatham, L. N., & Lam, R. W. (2022). Blue-Light Therapy for Seasonal and Non-Seasonal Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, *67*(10), 745–754. https://doi.org/10.1177/07067437221097903

Drevets, W. C., Bogers, W., & Raichle, M. E. (2002). Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism.

European Neuropsychopharmacology, *12*(6), 527–544. https://doi.org/10.1016/S0924-977X(02)00102-5

Duff, E. P., Cunnington, R., & Egan, G. F. (2007). REX: Response exploration for neuroimaging datasets. *Neuroinformatics*, *5*(4), 223–234. https://doi.org/10.1007/S12021-007-9001-Y/METRICS

Edwards, S. B., Ginsburgh, C. L., Henkel, C. K., & Stein, B. E. (1979). Sources of subcortical projections to the superior colliculus in the cat. *The Journal of Comparative Neurology*, *184*(2), 309–329. https://doi.org/10.1002/CNE.901840207

Emanuel, A. J., & Do, M. T. H. (2015). Melanopsin tristability for sustained and broadband phototransduction. *Neuron*, *85*(5), 1043–1055. https://doi.org/10.1016/J.NEURON.2015.02.011

Erdfelder, E., FAul, F., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behavior Research Methods*, *41*(4), 1149–1160. https://doi.org/10.3758/BRM.41.4.1149

Evangelisti, S., La Morgia, C., Testa, C., Manners, D. N., Brizi, L., Bianchini, C., Carbonelli, M., Barboni, P., Sadun, A. A., Tonon, C., Carelli, V., Vandewalle, G., & Lodi, R. (2021). Brain functional MRI responses to blue light stimulation in Leber's Hereditary Optic Neuropathy. *Biochemical Pharmacology*, 114488. https://doi.org/10.1016/j.bcp.2021.114488

Even, C., Schröder, C. M., Friedman, S., & Rouillon, F. (2008). Efficacy of light therapy in nonseasonal depression: A systematic review. In *Journal of Affective Disorders* (Vol. 108, Issues 1–2, pp. 11–23). J Affect Disord. https://doi.org/10.1016/j.jad.2007.09.008

Fernandez, D. C., Fogerson, P. M., Lazzerini Ospri, L., Thomsen, M. B., Layne, R. M., Severin, D., Zhan, J., Singer, J. H., Kirkwood, A., Zhao, H., Berson, D. M., & Hattar, S. (2018). Light Affects Mood and Learning through Distinct Retina-Brain Pathways. *Cell*, *175*(1), 71-84.e18. https://doi.org/10.1016/j.cell.2018.08.004

Fisher, P. M., Madsen, M. K., Mc Mahon, B., Holst, K. K., Andersen, S. B., Laursen, H. R., Hasholt, L. F., Siebner, H. R., & Knudsen, G. M. (2014). Three-week bright-light intervention has dose-related effects on threat-related corticolimbic reactivity and functional coupling. *Biological Psychiatry*, *76*(4), 332–339. https://doi.org/10.1016/J.BIOPSYCH.2013.11.031

Gaggioni, G., Maquet, P., Schmidt, C., Dijk, D., & Vandewalle, G. (2014). Neuroimaging, cognition, light and circadian rhythms. *Frontiers in Systems Neuroscience*, *8*(July), 126. https://doi.org/10.3389/fnsys.2014.00126

Gamlin, P. D. R., McDougal, D. H., Pokorny, J., Smith, V. C., Yau, K. W., & Dacey, D. M. (2007). Human and Macaque Pupil Responses Driven by Melanopsin-Containing Retinal Ganglion Cells. *Vision Research*, *47*(7), 946. https://doi.org/10.1016/J.VISRES.2006.12.015

Garcia-Saenz, A., De Miguel, A. S., Espinosa, A., Costas, L., Aragonés, N., Tonne, C., Moreno, V., Pérez-Gómez, B., Valentin, A., Pollán, M., Castaño-Vinyals, G., Aubé, M., & Kogevinas, M. (2020). Association between outdoor light-at-night exposure and colorectal cancer in Spain. *Epidemiology*, *31*(5), 718–727. https://doi.org/10.1097/EDE.0000000000001226

Garcia-Saenz, A., de Miguel, A. S., Espinosa, A., Valentin, A., Aragonés, N., Llorca, J., Amiano, P., Sánchez, V. M., Guevara, M., Capelo, R., Tardón, A., Peiró-Perez, R., Jiménez-Moleón, J. J., Roca-Barceló, A., Pérez-Gómez, B., Dierssen-Sotos, T., Fernández-Villa, T., Moreno-Iribas, C., Moreno, V., … Kogevinas, M. (2018). Evaluating the Association between Artificial Light-at-Night Exposure and Breast and Prostate Cancer Risk in Spain (MCC-Spain Study). *Environmental Health Perspectives*, *126*(4). https://doi.org/10.1289/EHP1837

Gasperetti, C. E., Dolsen, M. R., & Harvey, A. G. (2020). The influence of intensity and timing of daily light exposure on subjective and objective sleep in adolescents with an evening circadian preference. *Sleep Medicine*, *79*. https://doi.org/10.1016/j.sleep.2020.11.014

Geerdinck, L. M., Bikker, J. W., Meekes, G. J. B. M., de Ruyter, B., Leffers, P., Versteylen, M., Kuijpers, P. M. J. C., Giménez, M. C., Schlangen, L. J. M., & Herremans, H. (2016). Patient room lighting influences on sleep, appraisal and mood in hospitalized people. *Journal of Sleep Research*, *26*(2), 236–246. https://doi.org/10.1111/jsr.12470

Gilzenrat, M. S., Nieuwenhuis, S., Jepma, M., & Cohen, J. D. (2010). Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cognitive, Affective, & Behavioral Neuroscience 2010 10:2*, *10*(2), 252–269. https://doi.org/10.3758/CABN.10.2.252

Giménez, M. C., Stefani, O., Cajochen, C., Lang, D., Deuring, G., & Schlangen, L. J. M. (2022). Predicting melatonin suppression by light in humans: Unifying photoreceptor-based equivalent daylight illuminances, spectral composition, timing and duration of light exposure. *Journal of Pineal Research*, *72*(2). https://doi.org/10.1111/JPI.12786

Glickman, G., Byrne, B., Pineda, C., Hauck, W. W., & Brainard, G. C. (2006). Light therapy for Seasonal Affective Disorder with blue narrow-band light-emitting diodes (LEDs). *Biological Psychiatry*, *59*(6), 502–507. https://doi.org/10.1016/j.biopsych.2005.07.006

Gooley, J. J., Chamberlain, K., Smith, K. A., Khalsa, S. B. S., Rajaratnam, S. M. W., Van Reen, E., Zeitzer, J. M., Czeisler, C. A., & Lockley, S. W. (2011). Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. *The Journal of Clinical Endocrinology and Metabolism*, *96*(3), E463-72. https://doi.org/10.1210/jc.2010-2098

Gooley, J. J., Ho Mien, I., St. Hilaire, M. a., Yeo, S.-C., Chua, E. C.-P., van Reen, E., Hanley, C. J., Hull, J. T., Czeisler, C. a., & Lockley, S. W. (2012). Melanopsin and Rod-Cone Photoreceptors Play Different Roles in Mediating Pupillary Light Responses during Exposure to Continuous Light in Humans. *Journal of Neuroscience*, *32*(41), 14242–14253. https://doi.org/10.1523/JNEUROSCI.1321-12.2012

Grandjean, D., Sander, D., Pourtois, G., Schwartz, S., Seghier, M. L., Scherer, K. R., & Vuilleumier, P. (2005). The voices of wrath: Brain responses to angry prosody in meaningless speech. *Nature Neuroscience*, *8*(2), 145–146. https://doi.org/10.1038/nn1392

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., Reiss, A. L., & Schatzberg, A. F. (2007). Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. *Biological Psychiatry*, *62*(5), 429. https://doi.org/10.1016/J.BIOPSYCH.2006.09.020

Güler, A. D., Ecker, J. L., Lall, G. S., Haq, S., Altimus, C. M., Liao, H. W., Barnard, A. R., Cahill, H., Badea, T. C., Zhao, H., Hankins, M. W., Berson, D. M., Lucas, R. J., Yau, K. W., & Hattar, S.

(2008). Melanopsin cells are the principal conduits for rod-cone input to non-image-forming vision. *Nature*, *453*(7191), 102–105. https://doi.org/10.1038/nature06829

Hagan, J. J., Leslie, R. A., Patel, S., Evans, M. L., Wattam, T. A., Holmes, S., Benham, C. D., Taylor, S. G., Routledge, C., Hemmati, P., Munton, R. P., Ashmeade, T. E., Shah, A. S., Hatcher, J. P., Hatcher, P. D., Jones, D. N. C., Smith, M. I., Piper, D. C., Hunter, A. J., … Upton, N. (1999). Orexin A activates locus coeruleus cell firing and increases arousal in the rat. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(19), 10911–10916. https://doi.org/10.1073/PNAS.96.19.10911

Haris, E. M., Bryant, R. A., Williamson, T., & Korgaonkar, M. S. (2023). Functional connectivity of amygdala subnuclei in PTSD: a narrative review. *Molecular Psychiatry*, *28*(9), 3581–3594. https://doi.org/10.1038/S41380-023-02291-W

Hattar, S., Kumar, M., Park, A., Tong, P., Tung, J., Yau, K. W., & Berson, D. M. (2006). Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *Journal of Comparative Neurology*, *497*(3), 326–349. https://doi.org/10.1002/cne.20970

Hattar, S., Liao, H. W., Takao, M., Berson, D. M., & Yau, K. W. (2002). Melanopsin-containing retinal ganglion cells: Architecture, projections, and intrinsic photosensitivity. *Science*, *295*(5557), 1065–1070. https://doi.org/10.1126/science.1069609

Heath, M., Sutherland, C., Bartel, K., Gradisar, M., Williamson, P., Lovato, N., & Micic, G. (2014). Does one hour of bright or short-wavelength filtered tablet screenlight have a meaningful effect on adolescents' pre-bedtime alertness, sleep, and daytime functioning? *Chronobiology International*, *31*(4), 496–505. https://doi.org/10.3109/07420528.2013.872121

Herrera, C. G., Cadavieco, M. C., Jego, S., Ponomarenko, A., Korotkova, T., & Adamantidis, A. (2015). Hypothalamic feedforward inhibition of thalamocortical network controls arousal and consciousness. *Nature Neuroscience 2015 19:2*, *19*(2), 290–298. https://doi.org/10.1038/nn.4209

Hoopes, A., Mora, J. S., Dalca, A. V., Fischl, B., & Hoffmann, M. (2022). SynthStrip: skull-stripping for any brain image. *NeuroImage*, *260*, 119474. https://doi.org/10.1016/J.NEUROIMAGE.2022.119474

Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology*, *4*(2), 97–110.

Horvath, T. L., Peyron, C., Diano, S., Ivanov, A., Aston-Jones, G., Kilduff, T. S., & Van Den Pol, A. N. (1999). Hypocretin (orexin) activation and synaptic innervation of the locus coeruleus noradrenergic system. *Journal of Comparative Neurology*, *415*(2), 145–159. https://doi.org/10.1002/(SICI)1096-9861(19991213)415:2<145::AID-CNE1>3.0.CO;2-2

Houser, K. W., Boyce, P. R., Zeitzer, J. M., & Herf, M. (2020). Human-centric lighting: Myth, magic or metaphor? *Lighting Research and Technology*, 147715352095844. https://doi.org/10.1177/1477153520958448

Huang, L., Xi, Y., Peng, Y., Yang, Y., Huang, X., Fu, Y., Tao, Q., Xiao, J., Yuan, T., An, K., Zhao, H., Pu, M., Xu, F., Xue, T., Luo, M., So, K. F., & Ren, C. (2019). A Visual Circuit Related to Habenula

Underlies the Antidepressive Effects of Light Therapy. *Neuron*, *102*(1), 128-142.e8. https://doi.org/10.1016/j.neuron.2019.01.037

Huang, X., Tao, Q., & Ren, C. (2023). A Comprehensive Overview of the Neural Mechanisms of Light Therapy. *Neuroscience Bulletin*. https://doi.org/10.1007/S12264-023-01089-8

Hutton, C., Bork, A., Josephs, O., Deichmann, R., Ashburner, J., & Turner, R. (2002). Image distortion correction in fMRI: A quantitative evaluation. *NeuroImage*, *16*(1), 217–240. https://doi.org/10.1006/nimg.2001.1054

Jin, J., Chen, Q., Qiao, Q., Yang, L., Xiong, J., Xia, J., Hu, Z., & Chen, F. (2016). Orexin neurons in the lateral hypothalamus project to the medial prefrontal cortex with a rostro-caudal gradient. *Neuroscience Letters*, *621*, 9–14. https://doi.org/10.1016/J.NEULET.2016.04.002

Johns, M. W. (1993). Daytime sleepiness, snoring, and obstructive sleep apnea; The Epworth Sleepiness Scale. *Chest*, *103*(1), 30–36. https://doi.org/10.1378/chest.103.1.30

Jones, R. R. (2021). Exposure to artificial light at night and risk of cancer: where do we go from here? *British Journal of Cancer*. https://doi.org/10.1038/s41416-020-01231-7

Joshi, S., & Gold, J. I. (2020). Pupil Size as a Window on Neural Substrates of Cognition. *Trends in Cognitive Sciences*, *24*(6), 466–480. https://doi.org/10.1016/J.TICS.2020.03.005

Joshi, S., Li, Y., Kalwani, R. M., & Gold, J. I. (2016). Relationships between Pupil Diameter and Neuronal Activity in the Locus Coeruleus, Colliculi, and Cingulate Cortex. *Neuron*, *89*(1), 221–234. https://doi.org/10.1016/J.NEURON.2015.11.028

Kahneman, D., & Beatty, J. (1966). Pupil diameter and load on memory. *Science (New York, N.Y.)*, *154*(3756), 1583–1585. https://doi.org/10.1126/SCIENCE.154.3756.1583

Kain, M. P., Bolker, B. M., & McCoy, M. W. (2015). A practical guide and power analysis for GLMMs: Detecting among treatment variation in randomeffects. *PeerJ*, *2015*(9), e1226. https://doi.org/10.7717/PEERJ.1226/SUPP-1

Kaiser, C., Kaufmann, C., Leutritz, T., Arnold, Y. L., Speck, O., & Ullsperger, M. (2019). The human habenula is responsive to changes in luminance and circadian rhythm. *NeuroImage*, *189*, 581–588. https://doi.org/10.1016/j.neuroimage.2019.01.064

Kasper, L., Bollmann, S., Diaconescu, A. O., Hutton, C., Heinzle, J., Iglesias, S., Hauser, T. U., Sebold, M., Manjaly, Z. M., Pruessmann, K. P., & Stephan, K. E. (2017). The PhysIO Toolbox for Modeling Physiological Noise in fMRI Data. *Journal of Neuroscience Methods*, *276*, 56–72. https://doi.org/10.1016/J.JNEUMETH.2016.10.019

Kawasaki, A., Udry, M., El Wardani, M., & Münch, M. (2021). Can Extra Daytime Light Exposure Improve Well-Being and Sleep? A Pilot Study of Patients With Glaucoma. *Frontiers in Neurology*, *11*, 1839. https://doi.org/10.3389/FNEUR.2020.584479/BIBTEX

Keeler, C. E. (1927). IRIS MOVEMENTS IN BLIND MICE. *American Journal of Physiology-Legacy Content*, *81*(1), 107–112. https://doi.org/10.1152/ajplegacy.1927.81.1.107

Keis, O., Helbig, H., Streb, J., & Hille, K. (2014). Influence of blue-enriched classroom lighting on students' cognitive performance. *Trends in Neuroscience and Education*, *3*(3–4), 86–92. https://doi.org/10.1016/j.tine.2014.09.001

Keren, N. I., Lozar, C. T., Harris, K. C., Morgan, P. S., & Eckert, M. A. (2009). In vivo mapping of the human locus coeruleus. *NeuroImage*, *47*(4), 1261–1267. https://doi.org/10.1016/J.NEUROIMAGE.2009.06.012

Kiehl, K. A., & Liddle, P. F. (2003). Reproducibility of the hemodynamic response to auditory oddball stimuli: a six-week test-retest study. *Human Brain Mapping*, *18*(1), 42–52. https://doi.org/10.1002/HBM.10074

Kim, S. J., Lee, S. H., Suh, I. B., Jang, J. W., Jhoo, J. H., & Lee, J. H. (2021). Positive effect of timed blue-enriched white light on sleep and cognition in patients with mild and moderate Alzheimer's disease. *Scientific Reports*, *11*(1). https://doi.org/10.1038/S41598-021-89521-9

Knoop, M., Stefani, O., Bueno, B., Matusiak, B., Hobday, R., Wirz-Justice, A., Martiny, K., Kantermann, T., Aarts, M. P. J., Zemmouri, N., Appelt, S., & Norton, B. (2020). Daylight: What makes the difference? *Lighting Research and Technology*, *52*(3), 423–442. https://doi.org/10.1177/1477153519869758/ASSET/IMAGES/LARGE/10.1177_1477153519869758-FIG2.JPEG

Koenigs, M., & Grafman, J. (2009). The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural Brain Research*, *201*(2), 239–243. https://doi.org/10.1016/J.BBR.2009.03.004

Kompier, M. E., Smolders, K. C. H. J., & de Kort, Y. A. W. (2020). A systematic literature review on the rationale for and effects of dynamic light scenarios. *Building and Environment*, *186*, 107326. https://doi.org/10.1016/J.BUILDENV.2020.107326

Kong, Z., Liu, Q., Li, X., Hou, K., & Xing, Q. (2022). Indoor lighting effects on subjective impressions and mood states: A critical review. *Building and Environment*, *224*, 109591. https://doi.org/10.1016/J.BUILDENV.2022.109591

Koorengevel, K. M., Gordijn, M. C. M., Beersma, D. G. M., Meesters, Y., Den Boer, J. A., Van den Hoofdakker, R. H., & Daan, S. (2001). Extraocular light therapy in winter depression: A double-blind placebo-controlled study. *Biological Psychiatry*, *50*(9), 691–698. https://doi.org/10.1016/S0006-3223(01)01182-9

Lall, G. S., Revell, V. L., Momiji, H., Al Enezi, J., Altimus, C. M., Güler, A. D., Aguilar, C., Cameron, M. A., Allender, S., Hankins, M. W., & Lucas, R. J. (2010). Distinct contributions of rod, cone, and melanopsin photoreceptors to encoding irradiance. *Neuron*, *66*(3), 417–428. https://doi.org/10.1016/J.NEURON.2010.04.037

Lam, R. W., Levitt, A. J., Levitan, R. D., Michalak, E. E., Cheung, A. H., Morehouse, R., Ramasubbu, R., Yatham, L. N., & Tam, E. M. (2016). Efficacy of Bright Light Treatment, Fluoxetine, and the Combination in Patients With Nonseasonal Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, *73*(1), 56–63. https://doi.org/10.1001/JAMAPSYCHIATRY.2015.2235

Larsen, R. S., & Waters, J. (2018). Neuromodulatory Correlates of Pupil Dilation. *Frontiers in Neural Circuits*, *12*. https://doi.org/10.3389/FNCIR.2018.00021

Lavoie, M. P., Lam, R. W., Bouchard, G., Sasseville, A., Charron, M. C., Gagné, A. M., Tremblay, P., Filteau, M. J., & Hébert, M. (2009). Evidence of a Biological Effect of Light Therapy on the Retina of Patients with Seasonal Affective Disorder. *Biological Psychiatry*, *66*(3), 253–258. https://doi.org/10.1016/j.biopsych.2008.11.020

Lawrenson, J. G., Hull, C. C., & Downie, L. E. (2017). The effect of blue-light blocking spectacle lenses on visual performance, macular health and the sleep-wake cycle: a systematic review of the literature. *Ophthalmic and Physiological Optics*, *37*(6), 644–654. https://doi.org/10.1111/opo.12406

Lee, H. H., Tu, Y. C., & Yeh, S. L. (2021). In search of blue-light effects on cognitive control. *Scientific Reports 2021 11:1*, *11*(1), 1–13. https://doi.org/10.1038/s41598-021-94989-6

Legates, T. A., Altimus, C. M., Wang, H., Lee, H. K., Yang, S., Zhao, H., Kirkwood, A., Weber, E. T., & Hattar, S. (2012). Aberrant light directly impairs mood and learning through melanopsin-expressing neurons. *Nature*, *491*(7425), 594–598. https://doi.org/10.1038/nature11673

Lewy, A. J., Lefler, B. J., Emens, J. S., & Bauer, V. K. (2006). The circadian basis of winter depression. *Proceedings of the National Academy of Sciences*, *103*(19), 7414 LP – 7419. http://www.pnas.org/content/103/19/7414.abstract

Li, C. I., Maglinao, T. L., & Takahashi, L. K. (2004). Medial amygdala modulation of predator odor-induced unconditioned fear in the rat. *Behavioral Neuroscience*, *118*(2), 324–332. https://doi.org/10.1037/0735-7044.118.2.324

Li, Y., Ru, T., Chen, Q., Qian, L., Luo, X., & Zhou, G. (2021). Effects of illuminance and correlated color temperature of indoor light on emotion perception. *Scientific Reports 2021 11:1*, *11*(1), 1–12. https://doi.org/10.1038/s41598-021-93523-y

Liu, A. L., Liu, Y. F., Wang, G., Shao, Y. Q., Yu, C. X., Yang, Z., Zhou, Z. R., Han, X., Gong, X., Qian, K. W., Wang, L. Q., Ma, Y. Y., Zhong, Y. M., Weng, S. J., & Yang, X. L. (2022). The role of ipRGCs in ocular growth and myopia development. *Science Advances*, *8*(23), 9027. https://doi.org/10.1126/SCIADV.ABM9027

Liu, X., Zhou, Q., Lin, H., Wu, J., Wu, Z., Qu, S., & Bi, Y. (2019). The protective effects of blue light-blocking films with different shielding rates: A rat model study. *Translational Vision Science and Technology*, *8*(3). https://doi.org/10.1167/tvst.8.3.19

Lockley, S. W., Evans, E. E., Scheer, F. A. J. L., Brainard, G. C., Czeisler, C. A., & Aeschbach, D. (2006). Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. *Sleep*, *29*(2), 161–168. https://doi.org/10.1093/sleep/29.2.161

Lok, R., Smolders, K. C. H. J., Beersma, D. G. M., & de Kort, Y. A. W. (2018). Light, Alertness, and Alerting Effects of White Light: A Literature Overview. In *Journal of Biological Rhythms* (Vol. 33, Issue 6, pp. 589–601). SAGE Publications Inc. https://doi.org/10.1177/0748730418796443

Lucas, R. J., Lall, G. S., Allen, A. E., & Brown, T. M. (2012). How rod, cone, and melanopsin photoreceptors come together to enlighten the mammalian circadian clock. *Progress in Brain Research*, *199*, 1–18. https://doi.org/10.1016/B978-0-444-59427-3.00001-0

Lucas, R. J., Peirson, S. N., Berson, D. M., Brown, T. M., Cooper, H. M., Czeisler, C. A., Figueiro, M. G., Gamlin, P. D., Lockley, S. W., O'Hagan, J. B., Price, L. L. A., Provencio, I., Skene, D. J., & Brainard, G. C. (2014). Measuring and using light in the melanopsin age. *Trends in Neurosciences*, *37*(1), 1–9. https://doi.org/10.1016/j.tins.2013.10.004

Ma, S., Hangya, B., Leonard, C. S., Wisden, W., & Gundlach, A. L. (2018). Dual-transmitter systems regulating arousal, attention, learning and memory. *Neuroscience and Biobehavioral Reviews*, *85*, 21–33. https://doi.org/10.1016/J.NEUBIOREV.2017.07.009

Macé, É., Montaldo, G., Trenholm, S., Cowan, C., Brignall, A., Urban, A., & Roska, B. (2018). Whole-Brain Functional Ultrasound Imaging Reveals Brain Modules for Visuomotor Integration. *Neuron*, *100*(5), 1241-1251.e7. https://doi.org/10.1016/J.NEURON.2018.11.031

Magnusson, A., & Partonen, T. (2005). The diagnosis, symptomatology, and epidemiology of seasonal affective disorder. In *CNS Spectrums* (Vol. 10, Issue 8, pp. 625–634). MBL Communications. https://doi.org/10.1017/S1092852900019593

Maruani, J., & Geoffroy, P. A. (2022). Multi-Level Processes and Retina-Brain Pathways of Photic Regulation of Mood. *Journal of Clinical Medicine*, *11*(2). https://doi.org/10.3390/JCM11020448

Mathôt, S. (2018). Pupillometry: Psychology, physiology, and function. *Journal of Cognition*, *1*(1), 1–23. https://doi.org/10.5334/JOC.18/METRICS/

Mathôt, S., Schreij, D., & Theeuwes, J. (2012). OpenSesame: an open-source, graphical experiment builder for the social sciences. *Behavior Research Methods*, *44*(2), 314–324. https://doi.org/10.3758/S13428-011-0168-7

May, P. J. (2006). The mammalian superior colliculus: laminar structure and connections. *Progress in Brain Research*, *151*, 321–378. https://doi.org/10.1016/S0079-6123(05)51011-2

Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A., Silva, J. A., Tekell, J. L., Martin, C. C., Lancaster, J. L., & Fox, P. T. (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *The American Journal of Psychiatry*, *156*(5), 245–253. https://doi.org/10.1176/AJP.156.5.675

McAdams, H., Kaiser, E. A., Igdalova, A., Haggerty, E. B., Cucchiara, B., Brainard, D. H., & Aguirre, G. K. (2020). Selective amplification of ipRGC signals accounts for interictal photophobia in migraine. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(29), 17320–17329. https://doi.org/10.1073/pnas.2007402117

McDonald, A. J., & Augustine, J. R. (1993). Localization of GABA-like immunoreactivity in the monkey amygdala. *Neuroscience*, *52*(2), 281–294. https://doi.org/10.1016/0306-4522(93)90156-A

McGlashan, E. M., Poudel, G. R., Jamadar, S. D., Phillips, A. J. K., & Cain, S. W. (2021). Afraid of the dark: Light acutely suppresses activity in the human amygdala. *PLOS ONE*, *16*(6), e0252350. https://doi.org/10.1371/JOURNAL.PONE.0252350

Megemont, M., McBurney-Lin, J., & Yang, H. (2022). Pupil diameter is not an accurate realtime readout of locus coeruleus activity. *ELife*, *11*. https://doi.org/10.7554/ELIFE.70510

Melyan, Z., Tarttelin, E. E., Bellingham, J., Lucas, R. J., & Hankins, M. W. (2005). Addition of human melanopsin renders mammalian cells photoresponsive. *Nature*, *433*(7027), 741–745. https://doi.org/10.1038/nature03344

Meyer, C., Muto, V., Jaspar, M., Kussé, C., Lambot, E., Chellappa, S. L., Degueldre, C., Balteau, E., Luxen, A., Middleton, B., Archer, S. N., Collette, F., Dijk, D.-J., Phillips, C., Maquet, P., &

Vandewalle, G. (2016). Seasonality in human cognitive brain responses. *Proc. Natl. Acad. Sci. U. S. A.*, *113*(11), 3066–3071. https://doi.org/10.1073/pnas.1518129113

Milosavljevic, N., Cehajic-Kapetanovic, J., Procyk, C. A., & Lucas, R. J. (2016). Chemogenetic Activation of Melanopsin Retinal Ganglion Cells Induces Signatures of Arousal and/or Anxiety in Mice. *Current Biology*, *26*(17), 2358–2363. https://doi.org/10.1016/j.cub.2016.06.057

Mongrain, V., Carrier, J., & Dumont, M. (2006). Circadian and homeostatic sleep regulation in morningness-eveningness. *Journal of Sleep Research*, *15*(2), 162–166. https://doi.org/10.1111/J.1365-2869.2006.00532.X

Munch, M., Nowozin, C., Regente, J., Bes, F., De Zeeuw, J., Hadel, S., Wahnschaffe, A., & Kunz, D. (2016). Blue-Enriched Morning Light as a Countermeasure to Light at the Wrong Time: Effects on Cognition, Sleepiness, Sleep, and Circadian Phase. *Neuropsychobiology*, *74*(4), 207–218. https://doi.org/10.1159/000477093

Münch, M., Wirz-Justice, A., Brown, S. A., Kantermann, T., Martiny, K., Stefani, O., Vetter, C., Wright, K. P., Wulff, K., & Skene, D. J. (2020). The Role of Daylight for Humans: Gaps in Current Knowledge. *Clocks & Sleep*, *2*(1), 61–85. https://doi.org/10.3390/clockssleep2010008

Mure, L. S. (2021). Intrinsically Photosensitive Retinal Ganglion Cells of the Human Retina. *Frontiers in Neurology*, *12*. https://doi.org/10.3389/FNEUR.2021.636330

Mure, L. S., Cornut, P.-L., Rieux, C., Drouyer, E., Denis, P., Gronfier, C., & Cooper, H. M. (2009). Melanopsin Bistability: A Fly's Eye Technology in the Human Retina. *PLoS ONE*, *4*(6), e5991. https://doi.org/10.1371/journal.pone.0005991

Mure, L. S., Rieux, C., Hattar, S., & Cooper, H. M. (2007). Melanopsin-dependent nonvisual responses: Evidence for photopigment bistability in vivo. *Journal of Biological Rhythms*, *22*(5), 411–424. https://doi.org/10.1177/0748730407306043

Murphy, P. R., O'Connell, R. G., O'Sullivan, M., Robertson, I. H., & Balsters, J. H. (2014). Pupil diameter covaries with BOLD activity in human locus coeruleus. *Human Brain Mapping*, *35*(8), 4140–4154. https://doi.org/10.1002/hbm.22466

Nassar, M. R., Rumsey, K. M., Wilson, R. C., Parikh, K., Heasly, B., & Gold, J. I. (2012). Rational regulation of learning dynamics by pupil-linked arousal systems. *Nature Neuroscience 2012 15:7*, *15*(7), 1040–1046. https://doi.org/10.1038/nn.3130

Nixon, J. P., & Smale, L. (2007). A comparative analysis of the distribution of immunoreactive orexin A and B in the brains of nocturnal and diurnal rodents. *Behavioral and Brain Functions*, *3*, 28. https://doi.org/10.1186/1744-9081-3-28

O'Brien, K. R., Kober, T., Hagmann, P., Maeder, P., Marques, J., Lazeyras, F., Krueger, G., & Roche, A. (2014). Robust T1-Weighted Structural Brain Imaging and Morphometry at 7T Using MP2RAGE. *PLOS ONE*, *9*(6), e99676. https://doi.org/10.1371/JOURNAL.PONE.0099676

O'Hagan, J. B., Khazova, M., & Price, L. L. A. (2016). Low-energy light bulbs, computers, tablets and the blue light hazard. *Eye (Basingstoke)*, *30*(2), 230–233. https://doi.org/10.1038/eye.2015.261

Ono, D., Honma, K. ichi, & Honma, S. (2021). GABAergic mechanisms in the suprachiasmatic nucleus that influence circadian rhythm. *Journal of Neurochemistry*, *157*(1), 31–41. https://doi.org/10.1111/JNC.15012

Ono, D., Honma, K. ichi, Yanagawa, Y., Yamanaka, A., & Honma, S. (2018). Role of GABA in the regulation of the central circadian clock of the suprachiasmatic nucleus. *The Journal of Physiological Sciences : JPS*, *68*(4), 333–343. https://doi.org/10.1007/S12576-018-0604-X

Ouyang, X., Yang, J., Hong, Z., Wu, Y., Xie, Y., & Wang, G. (2020). Mechanisms of blue light-induced eye hazard and protective measures: a review. In *Biomedicine and Pharmacotherapy* (Vol. 130, p. 110577). Elsevier Masson SAS. https://doi.org/10.1016/j.biopha.2020.110577

Papamichael, C., Skene, D. J., & Revell, V. L. (2012). Human nonvisual responses to simultaneous presentation of blue and red monochromatic light. *Journal of Biological Rhythms*, *27*(1), 70–78. https://doi.org/10.1177/0748730411431447

Paparella, I., Campbell, I., Sharifpour, R., Beckers, E., Berger, A., Aizpurua, J. F. B., Koshmanova, E., Mortazavi, N., Talwar, P., Degueldre, C., Lamalle, L., Sherif, S., Phillips, C., Maquet, P., & Vandewalle, G. (2023). Light modulates task-dependent thalamo-cortical connectivity during an auditory attentional task. *Communications Biology 2023 6:1*, *6*(1), 1–10. https://doi.org/10.1038/s42003-023-05337-5

Penders, T. M., Stanciu, C. N., Schoemann, A. M., Ninan, P. T., Bloch, R., & Saeed, S. A. (2016). Bright Light Therapy as Augmentation of Pharmacotherapy for Treatment of Depression: A Systematic Review and Meta-Analysis. *The Primary Care Companion for CNS Disorders*, *18*(5), 26717. https://doi.org/10.4088/PCC.15R01906

Perrault, A. A., Bayer, L., Peuvrier, M., Afyouni, A., Ghisletta, P., Brockmann, C., Spiridon, M., Hulo Vesely, S., Haller, D. M., Pichon, S., Perrig, S., Schwartz, S., & Sterpenich, V. (2019). Reducing the use of screen electronic devices in the evening is associated with improved sleep and daytime vigilance in adolescents. *Sleep*, *42*(9). https://doi.org/10.1093/sleep/zsz125

Perrin, F., Peigneux, P., Fuchs, S., Verhaeghe, S., Laureys, S., Middleton, B., Degueldre, C., Del Fiore, G., Vandewalle, G., Balteau, E., Poirrier, R., Moreau, V., Luxen, A., Maquet, P., & Dijk, D. J. (2004). Nonvisual responses to light exposure in the human brain during the Circadian night. *Current Biology*, *14*(20), 1842–1846. https://doi.org/10.1016/j.cub.2004.09.082

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry*, *54*(5), 504–514. https://doi.org/10.1016/S0006-3223(03)00168-9

Pimputkar, S., Speck, J. S., Denbaars, S. P., & Nakamura, S. (2009). Prospects for LED lighting. In *Nature Photonics* (Vol. 3, Issue 4, pp. 180–182). Nature Publishing Group. https://doi.org/10.1038/nphoton.2009.32

Pjrek, E., Friedrich, M. E., Cambioli, L., Dold, M., Jäger, F., Komorowski, A., Lanzenberger, R., Kasper, S., & Winkler, D. (2020). The Efficacy of Light Therapy in the Treatment of Seasonal Affective Disorder: A Meta-Analysis of Randomized Controlled Trials. *Psychotherapy and Psychosomatics*, *89*(1), 17–24. https://doi.org/10.1159/000502891

Porrino, L. J., & Goldman-Rakic, P. S. (1982). Brainstem innervation of prefrontal and anterior cingulate cortex in the rhesus monkey revealed by retrograde transport of HRP. *The Journal of Comparative Neurology*, *205*(1), 63–76. https://doi.org/10.1002/CNE.902050107

Praschak-Rieder, N., & Willeit, M. (2012). Imaging of seasonal affective disorder and seasonality effects on serotonin and dopamine function in the human brain. *Current Topics in Behavioral Neurosciences*, *11*, 149–167. https://doi.org/10.1007/7854_2011_174

Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. In *Neuropsychopharmacology* (Vol. 35, Issue 1, pp. 192–216). Neuropsychopharmacology. https://doi.org/10.1038/npp.2009.104

Provencio, I., Rodriguez, I. R., Jiang, G., Hayes, W. P., Moreira, E. F., & Rollag, M. D. (2000). A novel human opsin in the inner retina. *Journal of Neuroscience*, *20*(2), 600–605. https://doi.org/10.1523/JNEUROSCI.20-02-00600.2000

Quirk, G. J., & Mueller, D. (2007). Neural Mechanisms of Extinction Learning and Retrieval. *Neuropsychopharmacology 2008 33:1*, *33*(1), 56–72. https://doi.org/10.1038/sj.npp.1301555

Rahman, S. A., St. Hilaire, M. A., Grant, L. K., Barger, L. K., Brainard, G. C., Czeisler, C. A., Klerman, E. B., & Lockley, S. W. (2022). Dynamic lighting schedules to facilitate circadian adaptation to shifted timing of sleep and wake. *Journal of Pineal Research*, *73*(1). https://doi.org/10.1111/JPI.12805

Rajkowski, J., Kubiak, P., & Aston-Jones, G. (1994). Locus coeruleus activity in monkey: Phasic and tonic changes are associated with altered vigilance. *Brain Research Bulletin*, *35*(5–6), 607–616. https://doi.org/10.1016/0361-9230(94)90175-9

Ranson, S. W., & Magoun, H. W. (1933). RESPIRATORY AND PUPILLARY REACTIONS: INDUCED BY ELECTRICAL STIMULATION OF THE HYPOTHALAMUS. *Archives of Neurology & Psychiatry*, *29*(6), 1179–1194. https://doi.org/10.1001/ARCHNEURPSYC.1933.02240120002001

Ricketts, E. J., Joyce, D. S., Rissman, A. J., Burgess, H. J., Colwell, C. S., Lack, L. C., & Gradisar, M. (2022). Electric lighting, adolescent sleep and circadian outcomes, and recommendations for improving light health. *Sleep Medicine Reviews*, *64*. https://doi.org/10.1016/J.SMRV.2022.101667

Riemersma-van der Lek, R. F., Swaab, D. F., Twisk, J., Hol, E. M., Hoogendijk, W. J., & Van Someren, E. J. (2008). Effect of Bright Light and Melatonin on Cognitive and Noncognitive Function in Elderly Residents of Group Care Facilities. *Jama*, *299*(22), 2642. https://doi.org/10.1001/jama.299.22.2642

Roecklein, K. A., Wong, P. M., Miller, M. A., Donofry, S. D., Kamarck, M. L., & Brainard, G. C. (2013). Melanopsin, Photosensitive Ganglion Cells, and Seasonal Affective Disorder. *Neurosci Biobehav Rev*, *37*(3), 229–239. https://doi.org/10.1016/j.neubiorev.2012.12.009

Rosenthal, N. E., & Bradt, G. W. T. (1984). Seasonal pattern assessment questionnaire (SPAQ). *National Institute of Mental Health, Bethesda, MD, USA*.

Rosenthal, N. E., Sack, D. A., Gillin, J. C., Lewy, A. J., Goodwin, F. K., Davenport, Y., Mueller, P. S., Newsome, D. A., & Wehr, T. A. (1984). Seasonal affective disorder. A description of the

syndrome and preliminary findings with light therapy. *Archives of General Psychiatry*, *41*(1), 72–80. https://doi.org/10.1001/ARCHPSYC.1984.01790120076010

Ru, T., Kompier, M. E., Chen, Q., Zhou, G., & Smolders, K. C. H. J. (2023). Temporal tuning of illuminance and spectrum: Effect of a full-day dynamic lighting pattern on well-being, performance and sleep in simulated office environment. *Building and Environment*, *228*, 109842. https://doi.org/10.1016/J.BUILDENV.2022.109842

Ruberg, F. L., Skene, D. J., Hanifin, J. P., Rollag, M. D., English, J., Arendt, J., & Brainard, G. C. (1996). Melatonin regulation in humans with color vision deficiencies. *The Journal of Clinical Endocrinology & Metabolism*, *81*(8), 2980–2985. https://doi.org/10.1210/jcem.81.8.8768862

Rufiange, M., Dumont, M., & Lachapelle, P. (2002). Correlating retinal function with melatonin secretion in subjects with an early or late circadian phase. *Investigative Ophthalmology and Visual Science*, *43*(7), 2491–2499.

Sabbah, S., Worden, M. S., Laniado, D. D., Berson, D. M., & Sanes, J. N. (2022). Luxotonic signals in human prefrontal cortex as a possible substrate for effects of light on mood and cognition. *Proceedings of the National Academy of Sciences of the United States of America*, *119*(28). https://doi.org/10.1073/PNAS.2118192119

Sah, P., Faber, E. S. L., De Armentia, M. L., & Power, J. (2003). The amygdaloid complex: Anatomy and physiology. *Physiological Reviews*, *83*(3), 803–834. https://doi.org/10.1152/PHYSREV.00002.2003/ASSET/IMAGES/MEDIUM/9J0330254002.JPEG

Sakurai, T. (2007). The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. *Nature Reviews. Neuroscience*, *8*(3), 171–181. https://doi.org/10.1038/NRN2092

Sander, D., Grandjean, D., Pourtois, G., Schwartz, S., Seghier, M. L., Scherer, K. R., & Vuilleumier, P. (2005). Emotion and attention interactions in social cognition: Brain regions involved in processing anger prosody. *NeuroImage*, *28*(4), 848–858. https://doi.org/10.1016/J.NEUROIMAGE.2005.06.023

Santhi, N., Thorne, H. C., Van Der Veen, D. R., Johnsen, S., Mills, S. L., Hommes, V., Schlangen, L. J. M., Archer, S. N., & Dijk, D. J. (2012). The spectral composition of evening light and individual differences in the suppression of melatonin and delay of sleep in humans. *Journal of Pineal Research*, *53*(1), 47–59. https://doi.org/10.1111/j.1600-079X.2011.00970.x

Scammell, T. E., Arrigoni, E., & Lipton, J. O. (2017). Neural Circuitry of Wakefulness and Sleep. In *Neuron* (Vol. 93, Issue 4, pp. 747–765). Cell Press. https://doi.org/10.1016/j.neuron.2017.01.014

Scammell, T. E., Jackson, A. C., Franks, N. P., Wisden, W., & Dauvilliers, Y. (2019). Histamine: neural circuits and new medications. *Sleep*, *42*(1), 1–8. https://doi.org/10.1093/SLEEP/ZSY183

Scheuermaier, K., Münch, M., Ronda, J. M., & Duffy, J. F. (2018). Improved cognitive morning performance in healthy older adults following blue-enriched light exposure on the previous evening. *Behavioural Brain Research*, *348*, 267–275. https://doi.org/10.1016/J.BBR.2018.04.021

Schoonderwoerd, R. A., de Rover, M., M Janse, J. A., Hirschler, L., Willemse, C. R., Scholten, L., Klop, I., van Berloo, S., P van Osch, M. J., Swaab, D. F., Meijer, J. H., & by Joseph Takahashi, E.

(2022). The photobiology of the human circadian clock. *Proceedings of the National Academy of Sciences*, *119*(13). https://doi.org/10.1073/PNAS.2118803119

Sexton, T. J., Golczak, M., Palczewski, K., & Van Gelder, R. N. (2012). Melanopsin is highly resistant to light and chemical bleaching in vivo. *Journal of Biological Chemistry*, *287*(25), 20888–20897. https://doi.org/10.1074/jbc.M111.325969

Sharifpour, R., Campbell, I., Beckers, E., Balda, F., Mortazavi, N., Koshmanova, E., Paparella, I., Sherif, S., Phillips, C., & Vandewalle, G. (2022). Pitfalls in Recording Bold Signal Responses to Light in Small Hypothalamic Nuclei Using Ultra-High-Field 7 Tesla MRI. *SSRN Electronic Journal*. https://doi.org/10.2139/SSRN.4174993

Sheppard, A. L., & Wolffsohn, J. S. (2018). Digital eye strain: prevalence, measurement and amelioration. *BMJ Open Ophthalmology*, *3*, 146. https://doi.org/10.1136/bmjophth-2018-000146

Silvani, M. I., Werder, R., & Perret, C. (2022). The influence of blue light on sleep, performance and wellbeing in young adults: A systematic review. *Frontiers in Physiology*, *13*. https://doi.org/10.3389/FPHYS.2022.943108

Šimić, G., Tkalčić, M., Vukić, V., Mulc, D., Španić, E., Šagud, M., Olucha-Bordonau, F. E., Vukšić, M., & Hof, P. R. (2021). Understanding Emotions: Origins and Roles of the Amygdala. *Biomolecules*, *11*(6). https://doi.org/10.3390/BIOM11060823

Singh, S., Downie, L. E., & Anderson, A. J. (2021). Do Blue-blocking Lenses Reduce Eye Strain From Extended Screen Time? A Double-Masked Randomized Controlled Trial. *American Journal of Ophthalmology*, *226*, 243–251. https://doi.org/10.1016/J.AJO.2021.02.010

Siraji, M. A., Kalavally, V., Schaefer, A., & Haque, S. (2022). Effects of Daytime Electric Light Exposure on Human Alertness and Higher Cognitive Functions: A Systematic Review. *Frontiers in Psychology*, *12*, 6079. https://doi.org/10.3389/FPSYG.2021.765750/BIBTEX

Smolders, K. C. H. J., Peeters, S. T., Vogels, I. M. L. C., & de Kort, Y. A. W. (2018). Investigation of Dose-Response Relationships for Effects of White Light Exposure on Correlates of Alertness and Executive Control during Regular Daytime Working Hours. *Journal of Biological Rhythms*, *33*(6), 649–661. https://doi.org/10.1177/0748730418796438

Sonoda, T., Li, J. Y., Hayes, N. W., Chan, J. C., Okabe, Y., Belin, S., Nawabi, H., & Schmidt, T. M. (2020). A noncanonical inhibitory circuit dampens behavioral sensitivity to light. *Science (New York, N.Y.)*, *368*(6490), 527–531. https://doi.org/10.1126/SCIENCE.AAY3152

Spindelegger, C., Stein, P., Wadsak, W., Fink, M., Mitterhauser, M., Moser, U., Savli, M., Mien, L. K., Akimova, E., Hahn, A., Willeit, M., Kletter, K., Kasper, S., & Lanzenberger, R. (2012). Light-dependent alteration of serotonin-1A receptor binding in cortical and subcortical limbic regions in the human brain. *The World Journal of Biological Psychiatry : The Official Journal of the World Federation of Societies of Biological Psychiatry*, *13*(6), 413–422. https://doi.org/10.3109/15622975.2011.630405

Spitschan, M., Barrionuevo, P. A., William Houser, K., M Schlangen, L. J., & A Price, L. L. (2018). The Lighting Environment, Its Metrology, and Non-visual Responses. *Frontiers in Neurology | Www.Frontiersin.Org*, *1*, 624861. https://doi.org/10.3389/fneur.2021.624861

Spitschan, M., Bock, A. S., Ryan, J., Frazzetta, G., Brainard, D. H., & Aguirre, G. K. (2017). The human visual cortex response to melanopsin-directed stimulation is accompanied by a distinct perceptual experience. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(46), 12291–12296. https://doi.org/10.1073/pnas.1711522114

Spitschan, M., Datta, R., Stern, A. M., Brainard, D. H., & Aguirre, G. K. (2016). Human visual cortex responses to rapid cone and melanopsin-directed flicker. *Journal of Neuroscience*, *36*(5), 1471–1482. https://doi.org/10.1523/JNEUROSCI.1932-15.2016

Spitschan, M., Lazar, R., Yetik, E., & Cajochen, C. (2019). No evidence for an S cone contribution to acute neuroendocrine and alerting responses to light. In *Current Biology* (Vol. 29, Issue 24, pp. R1297–R1298). Cell Press. https://doi.org/10.1016/j.cub.2019.11.031

Spitschan, M., Mead, J., Roos, C., Lowis, C., Griffiths, B., Mucur, P., Herf, M., Brown, T., Hanifin, J. P., Warfield, B., & Jefferson, T. (2021). *luox: novel open-access and open-source web platform for calculating and sharing physiologically relevant quantities for light and lighting [version 1; peer review: 2 approved]*. https://doi.org/10.12688/wellcomeopenres.16595.1

Spitschan, M., Reinhard, K., Flanders, N. R., Gamlin, P., Grünert, U., Lucas, R. J., & Mure, L. S. (2021). Intrinsically Photosensitive Retinal Ganglion Cells of the Human Retina. *Frontiers in Neurology | Www.Frontiersin.Org*, *1*, 636330. https://doi.org/10.3389/fneur.2021.636330

Stefani, O., Freyburger, M., Veitz, S., Basishvili, T., Meyer, M., Weibel, J., Kobayashi, K., Shirakawa, Y., & Cajochen, C. (2021). Changing color and intensity of LED lighting across the day impacts on circadian melatonin rhythms and sleep in healthy men. *Journal of Pineal Research*, e12714. https://doi.org/10.1111/jpi.12714

Steinhauer, S. R., Condray, R., & Pless, M. L. (2015). Pharmacological Isolation of Cognitive Components Influencing the Pupillary Light Reflex. *Journal of Ophthalmology*, *2015*. https://doi.org/10.1155/2015/179542

Steinhauer, S. R., Siegle, G. J., Condray, R., & Pless, M. (2004). Sympathetic and parasympathetic innervation of pupillary dilation during sustained processing. *International Journal of Psychophysiology*, *52*(1), 77–86. https://doi.org/10.1016/j.ijpsycho.2003.12.005

Strong, R. E., Marchant, B. K., Reimherr, F. W., Williams, E., Soni, P., & Mestas, R. (2009). Narrow-band blue-light treatment of seasonal affective disorder in adults and the influence of additional nonseasonal symptoms. *Depression and Anxiety*, *26*(3), 273–278. https://doi.org/10.1002/da.20538

Szabadi, E. (2018). Functional Organization of the Sympathetic Pathways Controlling the Pupil: Light-Inhibited and Light-Stimulated Pathways. *Frontiers in Neurology*, *9*, 419676. https://doi.org/10.3389/FNEUR.2018.01069/BIBTEX

Takahashi, K., Sobczak, F., Pais-Roldán, P., & Yu, X. (2023). Characterizing brain stage-dependent pupil dynamics based on lateral hypothalamic activity. *Cerebral Cortex*, *33*(21), 10736–10749. https://doi.org/10.1093/CERCOR/BHAD309

Terakita, A., Tsukamoto, H., Koyanagi, M., Sugahara, M., Yamashita, T., & Shichida, Y. (2008). Expression and comparative characterization of Gq-coupled invertebrate visual pigments and melanopsin. *Journal of Neurochemistry*, *105*(3), 883–890. https://doi.org/10.1111/J.1471-4159.2007.05184.X

Terman, M., & Terman, J. S. (2005). Light therapy for seasonal and nonseasonal depression: Efficacy, protocol, safety, and side effects. In *CNS Spectrums* (Vol. 10, Issue 8, pp. 647–663). MBL Communications. https://doi.org/10.1017/S1092852900019611

Thorne, H. C., Jones, K. H., Peters, S. P., Archer, S. N., & Dijk, D. J. (2009). Daily and seasonal variation in the spectral composition of light exposure in humans. *Chronobiology International*, *26*(5), 854–866. https://doi.org/10.1080/07420520903044315

Tow, S. L. C., Dubail, M., Tow, S. L. C., Aung, T., Tow, S. L. C., Aung, T., Gooley, J. J., & Hsieh, P. J. (2017). Cerebral neural correlates of differential melanopic photic stimulation in humans. *NeuroImage*, *146*, 763–769. https://doi.org/10.1016/j.neuroimage.2016.09.061

Tri, M., & Do, H. (2019). Melanopsin and the Intrinsically Photosensitive Retinal Ganglion Cells: Biophysics to Behavior. *Neuron*, *104*, 205–226. https://doi.org/10.1016/j.neuron.2019.07.016

Tse, N. Y., Ratheesh, A., Ganesan, S., Zalesky, A., & Cash, R. F. H. (2023). Functional dysconnectivity in youth depression: Systematic review, meta-analysis, and network-based integration. *Neuroscience and Biobehavioral Reviews*, *153*. https://doi.org/10.1016/J.NEUBIOREV.2023.105394

Tyszka, J. M., & Pauli, W. M. (2016). In vivo delineation of subdivisions of the human amygdaloid complex in a high-resolution group template. *Human Brain Mapping*, *37*(11), 3979–3998. https://doi.org/10.1002/HBM.23289

Valizadeh, P., Cattarinussi, G., Sambataro, F., Brambilla, P., & Delvecchio, G. (2023). Neuroimaging alterations associated with medication use in early-onset bipolar disorder: An updated review. *Journal of Affective Disorders*, *339*, 984–997. https://doi.org/10.1016/J.JAD.2023.07.098

Van Der Lely, S., Frey, S., Garbazza, C., Wirz-Justice, A., Jenni, O. G., Steiner, R., Wolf, S., Cajochen, C., Bromundt, V., & Schmidt, C. (2015). Blue blocker glasses as a countermeasure for alerting effects of evening light-emitting diode screen exposure in male teenagers. *Journal of Adolescent Health*, *56*(1), 113–119. https://doi.org/10.1016/j.jadohealth.2014.08.002

Van Norren, D., & Vos, J. J. (2015). Light damage to the retina: an historical approach. *Eye 2016 30:2*, *30*(2), 169–172. https://doi.org/10.1038/eye.2015.218

Vandewalle, G., Archer, S. N., Wuillaume, C., Balteau, E., Degueldre, C., Luxen, A., Dijk, D. J., & Maquet, P. (2011). Effects of light on cognitive brain responses depend on circadian phase and sleep homeostasis. *Journal of Biological Rhythms*, *26*(3), 249–259. https://doi.org/10.1177/0748730411401736

Vandewalle, G., Balteau, E., Phillips, C., Degueldre, C., Moreau, V., Sterpenich, V., Albouy, G., Darsaud, A., Desseilles, M., Dang-Vu, T. T., Peigneux, P., Luxen, A., Dijk, D. J., & Maquet, P. (2006). Daytime Light Exposure Dynamically Enhances Brain Responses. *Current Biology*, *16*(16), 1616–1621. https://doi.org/10.1016/j.cub.2006.06.031

Vandewalle, G., Collignon, O., Hull, J. T., Daneault, V., Albouy, G., Lepore, F., Phillips, C., Doyon, J., Czeisler, C. A., Dumont, M., Lockley, S. W., & Carrier, J. (2013). Blue Light Stimulates Cognitive Brain Activity in Visually Blind Individuals HHS Public Access. *J Cogn Neurosci*, *25*(12), 2072–2085. https://doi.org/10.1162/jocn_a_00450

Vandewalle, G., Gais, S., Schabus, M., Balteau, E., Carrier, J., Darsaud, A., Sterpenich, V., Albouy, G., Dijk, D. J., & Maquet, P. (2007). Wavelength-dependent modulation of brain responses to a working memory task by daytime light exposure. *Cerebral Cortex (New York, N.Y. : 1991)*, *17*(12), 2788–2795. https://doi.org/10.1093/cercor/bhm007

Vandewalle, G., Hébert, M., Beaulieu, C., Richard, L., Daneault, V., Garon, M. Lou, Leblanc, J., Grandjean, D., Maquet, P., Schwartz, S., Dumont, M., Doyon, J., & Carrier, J. (2011). Abnormal hypothalamic response to light in seasonal affective disorder. *Biological Psychiatry*, *70*(10), 954–961. https://doi.org/10.1016/j.biopsych.2011.06.022

Vandewalle, G., Maquet, P., & Dijk, D. J. (2009). Light as a modulator of cognitive brain function. In *Trends in Cognitive Sciences* (Vol. 13, Issue 10, pp. 429–438). Elsevier Ltd. https://doi.org/10.1016/j.tics.2009.07.004

Vandewalle, G., Schmidt, C., Albouy, G., Sterpenich, V., Darsaud, A., Rauchs, G., Berken, P. Y., Balteau, E., Dagueldre, C., Luxen, A., Maquet, P., & Dijk, D. J. (2007). Brain responses to violet, blue, and green monochromatic light exposures in humans: Prominent role of blue light and the brainstem. *PLoS ONE*, *2*(11), e1247. https://doi.org/10.1371/journal.pone.0001247

Vandewalle, G., Schwartz, S., Grandjean, D., Wuillaume, C., Balteau, E., Degueldre, C., Schabus, M., Phillips, C., Luxen, A., Dijk, D. J., & Maquet, P. (2010). Spectral quality of light modulates emotional brain responses in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(45), 19549–19554. https://doi.org/10.1073/pnas.1010180107

Vandewalle, G., van Ackeren, M. J., Daneault, V., Hull, J. T., Albouy, G., Lepore, F., Doyon, J., Czeisler, C. A., Dumont, M., Carrier, J., Lockley, S. W., & Collignon, O. (2018). Light modulates oscillatory alpha activity in the occipital cortex of totally visually blind individuals with intact non-image-forming photoreception. *Scientific Reports*, *8*(1), 1–9. https://doi.org/10.1038/s41598-018-35400-9

Vann, S. D. (2010). Re-evaluating the role of the mammillary bodies in memory. *Neuropsychologia*, *48*(8), 2316–2327. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2009.10.019

Varazzani, C., San-Galli, A., Gilardeau, S., & Bouret, S. (2015). Noradrenaline and dopamine neurons in the reward/effort trade-off: a direct electrophysiological comparison in behaving monkeys. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *35*(20), 7866–7877. https://doi.org/10.1523/JNEUROSCI.0454-15.2015

Veitch, J. (2023). *CIE Research Strategy 2023*. https://doi.org/10.25039/VUDFG44Z

Vetter, C., Pattison, P. M., Houser, K., Herf, M., Phillips, A. J. K., Wright, K. P., Skene, D. J., Brainard, G. C., Boivin, D. B., & Glickman, G. (2021). A Review of Human Physiological Responses to Light: Implications for the Development of Integrative Lighting Solutions. *Https://Doi.Org/10.1080/15502724.2021.1872383*, *18*(3), 387–414. https://doi.org/10.1080/15502724.2021.1872383

Vicente-Tejedor, J., Marchena, M., Ramírez, L., García-Ayuso, D., Gómez-Vicente, V., Sánchez-Ramos, C., de la Villa, P., & Germain, F. (2018). Removal of the blue component of light significantly decreases retinal damage after high intensity exposure. *PLOS ONE*, *13*(3), e0194218. https://doi.org/10.1371/journal.pone.0194218

Viénot, F., Brettel, H., Dang, T.-V., & Le Rohellec, J. (2012). Domain of metamers exciting intrinsically photosensitive retinal ganglion cells (ipRGCs) and rods. *Journal of the Optical Society of America A*, *29*(2), A366. https://doi.org/10.1364/josaa.29.00a366

Vinkers, C. H., Bijlsma, E. Y., Houtepen, L. C., Westphal, K. G. C., Veening, J. G., Groenink, L., & Olivier, B. (2010). Medial amygdala lesions differentially influence stress responsivity and sensorimotor gating in rats. *Physiology & Behavior*, *99*(3), 395–401. https://doi.org/10.1016/J.PHYSBEH.2009.12.006

Viola, A. U., James, L. M., Schlangen, L. J. M., & Dijk, D. J. (2008). Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scandinavian Journal of Work, Environment and Health*, *34*(4), 297–306. https://doi.org/10.5271/sjweh.1268

Wang, C. A., Boehnke, S. E., White, B. J., & Munoz, D. P. (2012). Microstimulation of the Monkey Superior Colliculus Induces Pupil Dilation Without Evoking Saccades. *The Journal of Neuroscience*, *32*(11), 3629. https://doi.org/10.1523/JNEUROSCI.5512-11.2012

Wang, C. A., & Munoz, D. P. (2015). A circuit for pupil orienting responses: implications for cognitive modulation of pupil size. *Current Opinion in Neurobiology*, *33*, 134–140. https://doi.org/10.1016/J.CONB.2015.03.018

Wang, G., Liu, Y. F., Yang, Z., Yu, C. X., Tong, Q., Tang, Y. L., Shao, Y. Q., Wang, L. Q., Xu, X., Cao, H., Zhang, Y. Q., Zhong, Y. M., Weng, S. J., & Yang, X. L. (2023). Short-term acute bright light exposure induces a prolonged anxiogenic effect in mice via a retinal ipRGC-CeA circuit. *Science Advances*, *9*(12). https://doi.org/10.1126/SCIADV.ADF4651

Wang, Y., Naylor, G., Kramer, S. E., Zekveld, A. A., Wendt, D., Ohlenforst, B., & Lunner, T. (2018). Relations Between Self-Reported Daily-Life Fatigue, Hearing Status, and Pupil Dilation During a Speech Perception in Noise Task. *Ear and Hearing*, *39*(3), 573–582. https://doi.org/10.1097/AUD.0000000000000512

Wässle, H. (2004). Parallel processing in the mammalian retina. In *Nature Reviews Neuroscience* (Vol. 5, Issue 10, pp. 747–757). https://doi.org/10.1038/nrn1497

Weiskopf, N., Mohammadi, S., Lutti, A., & Callaghan, M. F. (2015). Advances in MRI-based computational neuroanatomy: From morphometry to in-vivo histology. In *Current Opinion in Neurology* (Vol. 28, Issue 4, pp. 313–322). Lippincott Williams and Wilkins. https://doi.org/10.1097/WCO.0000000000000222

Whalen, P. J., & Phelps, E. A. (2009). The human amygdala. In Whalen Paul J; Phelps Elizabeth A. (Ed.), *The Human Amygdala* (1st ed.). Guilford Press. https://nyuscholars.nyu.edu/en/publications/the-human-amygdala

Wirz-Justice, A., Skene, D. J., & Münch, M. (2020). The relevance of daylight for humans. In *Biochemical Pharmacology* (p. 114304). Elsevier Inc. https://doi.org/10.1016/j.bcp.2020.114304

Wong, N. A., & Bahmani, H. (2022). A review of the current state of research on artificial blue light safety as it applies to digital devices. *Heliyon*, *8*(8). https://doi.org/10.1016/J.HELIYON.2022.E10282

Wright, K. P., McHill, A. W., Birks, B. R., Griffin, B. R., Rusterholz, T., & Chinoy, E. D. (2013). Entrainment of the human circadian clock to the natural light-dark cycle. *Current Biology*, *23*(16), 1554–1558. https://doi.org/10.1016/j.cub.2013.06.039

Xiang, Z. Y., & Zou, H. D. (2020). Recent Epidemiology Study Data of Myopia. In *Journal of Ophthalmology* (Vol. 2020). Hindawi Limited. https://doi.org/10.1155/2020/4395278

Xiong, S., Sankaridurg, P., Naduvilath, T., Zang, J., Zou, H., Zhu, J., Lv, M., He, X., & Xu, X. (2017). Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. *Acta Ophthalmologica*, *95*(6), 551–566. https://doi.org/10.1111/AOS.13403

Yelden, K., James, L. M., Duport, S., Kempny, A., Farmer, S. F., Leff, A. P., & Playford, E. D. (2022). A simple intervention for disorders of consciousness- is there a light at the end of the tunnel? *Frontiers in Neurology*, *13*, 1534. https://doi.org/10.3389/FNEUR.2022.824880/BIBTEX

Zaidi, F. H., Hull, J. T., Peirson, S. N. N., Wulff, K., Aeschbach, D., Gooley, J. J., Brainard, G. C. C., Gregory-Evans, K., Rizzo, J. F. F., Czeisler, C. A., Foster, R. G. G., Moseley, M. J., & Lockley, S. W. (2007). Short-Wavelength Light Sensitivity of Circadian, Pupillary, and Visual Awareness in Humans Lacking an Outer Retina. *Current Biology*, *17*(24), 2122–2128. https://doi.org/10.1016/j.cub.2007.11.034

Zeitzer, J. M. (2013). Control of sleep and wakefulness in health and disease. *Progress in Molecular Biology and Translational Science*, *119*, 137–154. https://doi.org/10.1016/B978-0-12-396971-2.00006-3

Zhang, C., Zhu, Z., Zhao, J., Li, Y., Zhang, Z., & Zheng, Y. (2023). Ubiquitous light-emitting diodes: Potential threats to retinal circadian rhythms and refractive development. *Science of The Total Environment*, *862*, 160809. https://doi.org/10.1016/J.SCITOTENV.2022.160809

Zhang, R., & Volkow, N. D. (2023). Seasonality of brain function: role in psychiatric disorders. *Translational Psychiatry 2023 13:1*, *13*(1), 1–11. https://doi.org/10.1038/s41398-023-02365-x

Zhou, H., Zhang, H., Yu, A., & Xie, J. (2018). Association between sunlight exposure and risk of age-related macular degeneration: A meta-analysis. *BMC Ophthalmology*, *18*(1), 1–8. https://doi.org/10.1186/S12886-018-1004-Y/FIGURES/3

Ziegelberger, G., Miller, S. A., O'Hagan, J., Okuno, T., Schulmeister, K., Sliney, D., Stuck, B., Croft, R., Feychting, M., Green, A. C., Hirata, A., D'Inzeo, G., Marino, C., Oftedal, G., van Rongen, E., Röösli, M., Sienkiewicz, Z., & Watanabe, S. (2020). Light-emitting diodes (LEDS): Implications for safety. *Health Physics*, *118*(5), 549–561. https://doi.org/10.1097/HP.0000000000001259