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FACULTY OF MEDICINE

Multimodal Investigation of Non-Image Forming Effects of Light on the Brain: Impact of Time of Day and Developmental Stage

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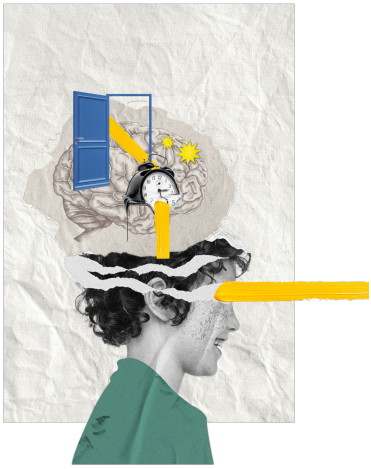

Supervisor:
Prof. Gilles Vandewalle

A thesis submitted in partial fulfilment of the requirements for

the degree of Doctor of Philosophy in Biomedical Sciences and Pharmacology

Academic year 2024-2025

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To those whose presence I cherish,
whose support has made this journey possible...

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 express my heartfelt gratitude to my wonderful supervisor, Dr. Gilles Vandewalle. Gilles, you've consistently supported me and my ambitious career goals, and your encouragement has been invaluable throughout my journey. Thank you for welcoming me to Belgium to start a new chapter of my life and for giving me the opportunity to work at the Cyclotron Research Center! You've been a calming presence during stressful times, reassuring me when I needed it most. I truly appreciate the time you dedicated to my work—your feedback has made all the difference.

I would also like to express my appreciation to the members of my jury: Dr. Christian Cajochen and Dr. Valérie Goffaux. Thank you for taking the time to review and evaluate my research from different perspectives. I also want to acknowledge my thesis committee members: Dr. Pierre Macquet, Dr. Christophe Phillips, and Dr. Mohamed Ali Bahri. Your discussions, questions, and guidance have been invaluable in helping me complete my project. I look forward to the opportunity to discuss my work with all of you.

Special thanks to my lovely lab members. This work would not have been possible without your help and continued support. To begin with, I want to thank you, Islay, for initiating the project. Your considerable effort in setting up the fMRI protocol, especially during the challenging times of COVID, was invaluable.

Ilenia, you were more than just a colleague; you were my officemate, someone I could trust and always rely on when I needed to talk. I appreciate all your help and support. Even with projects that weren't directly related to your own work, you dedicated your time to help, demonstrating what it truly means to be a team member. I really appreciate your support.

Elise, Alexandre and Katya, thank you for your invaluable help in times of need.

I would like to extend my thanks to Fermin and John, who joined the team a bit later. Fermin, I truly appreciate your assistance with data acquisition. John, thank you for your invaluable help with both acquisitions and recruitment for the TEENLIGHT project. Your contributions were crucial in helping us recruit enough teenagers for the study. I would also like to say thank you to Erik and Catherine for the recruitment and helping with data acquisition. I also want to acknowledge Zoe and Sara, the master's students who contributed to the data acquisition process.

The TEENLIGHT protocol was quite demanding, and without the support of my amazing colleagues, I couldn't have managed it.

Nasrin and Sepehr, you were not just my colleagues but also my great friends here. We've all faced tough times, being far from our families and loved ones during challenging situations in our home country. In those moments, we had only each other, and your presence was incredibly supportive. You were the ones who truly understood, and we made it through those days together. You have always been there for me during the toughest moments of my life, and I can't thank you enough for your support.

Mina and Alireza, you know just how much our friendship means to me. You are not only my friends but also my second family here, and I feel incredibly fortunate to have you in my life. You have always been understanding and thoughtful, supporting me during my difficult times. I can't thank you enough. You are, and always will be, my best friends.

Finally, my **greatest** thanks to my family for everything they have done for me. Mom, your dedication to us has meant the world; You have always put us first. Dad, your constant support and guidance have been a true inspiration in my life. Both of you, your pride in my achievements has motivated me every step of the way. And to my twin sister Shiva and my brother Hamidreza, your encouragement and backing have been invaluable. It has not been easy being far away from you, especially during tough times, but you have always been there for me. I could not have achieved this without each of you in my family by my side.

Abstract

Lighting can significantly influence various aspects of our life, including health, performance, and behavior. Inappropriate lighting is associated with numerous challenges in these areas, while appropriate lighting can enhance well-being and functionality. Key factors such as timing, intensity, and spectral composition play crucial roles in determining appropriate versus inappropriate lighting conditions. The human brain processes light via two pathways: the classical visual system, responsible for image formation, and the non-image forming (NIF) system, which reacts to environmental light levels. The NIF system is especially sensitive to shorter blue wavelengths (~480 nm), influencing circadian rhythms, neuroendocrine functions, and neurobehavioral responses.

Over the years, lighting technology has transitioned from incandescent and fluorescent bulbs to energy-efficient light emitting diodes (LEDs). This shift has altered the spectral composition of indoor lighting, increasing the prevalence of blue light, as typical "white" LEDs peak between 440-460 nm. Moreover, the widespread use of LEDs has extended our exposure to blue-enriched light into biological night, which can be detrimental to health by disrupting circadian rhythms and other physiological processes. Given these developments, it is essential to understand how light interacts with the brain and influences its functions beyond vision. Furthermore, the understanding of the NIF system, combined with advancements in LED technology, has given rise to the concept of integrative lighting, which aims to optimize both visual clarity and biological effects. To maximize the health benefits of integrative lighting and minimize adverse impacts, it is essential to investigate how light affects brain function and how factors like age and timing of exposure modulate these effects.

To further explore the NIF effects of light on human brain, we employed ultra-high-field 7 Tesla (UHF 7T) functional magnetic resonance imaging (fMRI) for its high resolution, allowing us to image small subcortical structures affected by light, such as the hypothalamus and thalamus nuclei. Healthy adolescents and young adults participated in an fMRI protocol at various times of day while exposed to different light intensities and engaged in auditory cognitive tasks. Additionally, we used transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) to assess NIF effects at the cortical level, with participants completing a TMS-EEG protocol in the afternoon under varying light conditions.

In this thesis, we initially focused on understanding how light affects one of its primary targets: the hypothalamus. This involved two studies. We first investigated whether there were regional variations in response to light exposure within the human hypothalamus during cognitive tasks in

the morning among young adults. The results indicated distinct response patterns to increasing light levels across different regions of the hypothalamus. Notably, higher light levels led to increased activity in the posterior hypothalamus, while the anterior and ventral regions showed reduced activity. This suggests that the posterior hypothalamus may be a key area where light stimulates cognition and alertness, potentially through mechanisms involving orexin and histamine signaling.

We expanded this investigation by doing fMRI in the evening and including adolescents to assess how time-of-day and developmental age influence hypothalamic response dynamics. The findings reinforced the anterior-posterior gradient observed in response to varying light levels. Specifically, increased illuminance continued to activate the posterior hypothalamus while decreasing activity in the anterior and ventral regions during the evening and in adolescents. Time-of-day did not alter the hypothalamic response, while age did; adolescents exhibited a stronger response to light compared to adults, showing more significant deactivation in the anterior and ventral regions. This suggests greater sensitivity in adolescents and highlights other functional differences related to age.

Next, we investigated the thalamus' established role in NIF functions, as highlighted in the literature. Given its key position as a central hub in the brain' signaling network, the thalamus likely plays a crucial role in relaying NIF signals to the cortex, thereby influencing alertness and cognitive function. In this context, we hypothesized that the impact of light on cognition might extends beyond altering regional activity to also affect functional connectivity throughout the brain.

Our third study focused therefore on how light affects functional connectivity between the thalamus and two cortical regions involved in executive functions, particularly working memory. We examined how light modulates connectivity among these areas while considering age and time-of-day differences. Our findings revealed that moderate illuminance blue-enriched light enhanced a cortico-cortical connectivity across all groups. Interestingly, low illuminance orange light also strengthened a connectivity from the thalamus to one of the cortical regions. Additionally, both time-of-day and age influenced how light affected connectivity. For instance, the highest illuminance blue-enriched light strengthened the thalamus-to-medial frontal gyrus connectivity in the morning among adults. Moreover, moderate illuminance blue-enriched light positively impacted the thalamus-to-supramarginal gyrus connectivity in adolescents. This investigation deepens our understanding of the complex neural mechanisms by which light affects cognitive processes and highlights the role of time-of-day and age.

In the final study, we extended our investigation to cortical level by using TMS-EEG to examine, for the first time, the effect of light on cortical excitability. Our findings revealed a distinct response between adolescents and adults. While cortical excitability in adults followed an apparent inverted U-shaped function with increasing illuminance, light showed no effect on cortical excitability in adolescents. These results further emphasize the different sensitivity of adolescents to light.

Overall, this thesis explores aspects of the brain circuitry involved in how light affects cognitive functions. It emphasizes the significance of factors like time-of-day and age, highlighting that a deeper understanding of how light influences cognitive processes and its modulatory factors can lead to integrative lighting solutions that promote health and well-being in the future.

Resume

L'éclairage peut influencer de manière significative divers aspects de notre vie, y compris la santé, la performance et le comportement. Un éclairage inapproprié est associé à de nombreux problemes, tandis qu'un éclairage approprié peut améliorer le bien-être. Des facteurs clés tels que le moment de l'exposition, l'intensité et la composition spectrale jouent un rôle crucial pour déterminer les conditions d'éclairage appropriées ou inappropriées. La rétine humaine traite la lumière via deux voies : le système visuel classique, responsable de la formation d'images, et le système non-visuel (NIF), qui réagit aux niveaux de lumière environnementale. Le système NIF est particulièrement sensible aux longueurs d'onde bleues, plus courtes (~480 nm), influençant les rythmes circadiens, les fonctions neuroendocrines et les réponses neurocomportementales.

Au fil des ans, l'éclairage est passée des ampoules à incandescence et fluorescentes aux diodes électroluminescentes écoénergétiques (LED). Ce changement a modifié la composition spectrale de l'éclairage intérieur, augmentant la quantite de lumière bleue, car les LED "blanches" typiques ont des pics entre 440 et 460 nm. De plus, l'utilisation généralisée des LED a étendu notre exposition à la lumière enrichie en bleu durant la nuit biologique, ce qui peut nuire à la santé en perturbant les rythmes circadiens et d'autres processus physiologiques. Étant donné ces évolutions, il est essentiel de comprendre comment la lumière interagit avec le cerveau et influence ses fonctions au-delà de la vision. De plus, la compréhension du système NIF, combinée aux avancées technologiques des LED, a donné naissance au concept d'éclairage intégratif, qui vise à optimiser à la fois la vision et les effets biologiques. Pour maximiser les bienfaits pour la santé de l'éclairage intégratif et minimiser ses effets néfastes, il est essentiel d'étudier comment la lumière affecte le cerveau et comment des facteurs tels que l'âge et l'heure de la journée modulent ces effets.

Pour explorer plus en détail les effets NIF de la lumière sur le cerveau humain, nous avons utilisé l'imagerie par résonance magnétique fonctionnelle (IRMf) à champ ultra-élevé de 7 Tesla (UHF 7T) en raison de sa haute résolution, nous permettant d'imager les petites structures sous-corticales affectées par la lumière, comme l'hypothalamus et les noyaux du thalamus. Des adolescents et des jeunes adultes en bonne santé ont participé à un protocole IRMf à différents moments de la journée tout en étant exposés à différentes intensités lumineuses et en accomplissant des tâches cognitives auditives. De plus, nous avons utilisé la stimulation magnétique transcrânienne combinée à l'électroencéphalographie (TMS-EEG) pour évaluer les effets NIF au niveau cortical, les participants ayant complété un protocole TMS-EEG l'après-midi sous diverses conditions

lumineuses.

Dans ma thèse, nous avons d'abord cherché à comprendre dans deux etudes comment la lumière affecte l'une de ses principales cibles : l'hypothalamus. Nous avons d'abord examiné s'il existait des variations régionales de la réponse à l'exposition à la lumière au sein de l'hypothalamus humain lors de tâches cognitives le matin chez les jeunes adultes. Les résultats ont montré des schémas de réponse distincts en fonction des niveaux de lumière croissants dans différentes régions de l'hypothalamus. Notamment, des niveaux de lumière plus élevés ont entraîné une augmentation de l'activité dans l'hypothalamus postérieur, tandis que les régions antérieure et ventrale ont montré une activité réduite. Cela suggère que l'hypothalamus postérieur pourrait être une zone clé via laquelle la lumière stimule la cognition et l'éveil, potentiellement par des mécanismes impliquant la signalisation orexinergique et/ou histaminergique.

Nous avons élargi cette investigation en réalisant des IRMf le soir et en incluant des adolescents pour évaluer comment l'heure de la journée et l'âge développemental influencent la dynamique des réponses de l'hypothalamus. Les résultats ont confirmé le gradient antéro-postérieur observé en réponse à des niveaux de lumière variables. En particulier, une augmentation de l'éclairement a continué d'activer l'hypothalamus postérieur tout en diminuant l'activité des régions antérieure et ventrale, pendant la soirée et chez les adolescents. L'heure de la journée n'a pas influencé la réponse de l'hypothalamus, tandis que l'âge a eu un impact; les adolescents ont montré une réponse plus forte à la lumière que les adultes, avec une déactivation plus marquée des régions antérieure et ventrale. Cela suggère une plus grande sensibilité chez les adolescents et met en évidence des différences fonctionnelles liées à l'âge.

Ensuite, nous avons étudié le rôle du thalamus dans les fonctions NIF, tel qu'il est décrit dans la littérature. Étant donné sa position centrale dans le réseau de signalisation du cerveau, le thalamus joue probablement un rôle crucial dans la transmission des signaux NIF vers le cortex, influençant ainsi l'éveil et les fonctions cognitives. Dans ce contexte, nous avons émis l'hypothèse que l'impact de la lumière sur la cognition pourrait aller au-delà de la simple altération de l'activité régionale, en affectant également la connectivité à travers le cerveau.

Notre troisième étude s'est donc concentrée sur la façon dont la lumière affecte la connectivité fonctionnelle entre le thalamus et deux régions corticales impliquées dans les fonctions exécutives, en particulier la mémoire de travail. Nous avons examiné comment la lumière module la connectivité entre ces zones tout en prenant en compte les différences d'âge et d'heure de la journée. Nos résultats ont révélé que la lumière bleue modérément enrichie augmentait la connectivité cortico-corticale à travers tous les groupes. Fait intéressant, une lumière orange

faible a également renforcé la connectivité du thalamus vers une des régions corticales. De plus, tant l'heure de la journée que l'âge ont influencé la manière dont la lumière affectait la connectivité. Par exemple, la lumière enrichie en bleu la plus forte a renforcé la connectivité entre le thalamus et le gyrus frontal médial le matin chez les adultes. De plus, une lumière bleue modérément enrichie a positivement impacté la connectivité entre le thalamus et le gyrus supramarginal chez les adolescents. Cette étude approfondit notre compréhension des mécanismes neuronaux complexes par lesquels la lumière affecte les processus cognitifs et met en lumière le rôle du moment de la journée et de l'âge.

Dans la dernière étude, nous avons élargi notre investigation au niveau cortical en utilisant la TMS-EEG pour examiner, pour la première fois, l'effet de la lumière sur l'excitabilité corticale. Nos résultats ont révélé une réponse distincte entre les adolescents et les adultes. Alors que l'excitabilité corticale chez les adultes suivait une probable fonction en forme de U inversé avec l'augmentation de l'éclairement, la lumière n'avait aucun effet sur l'excitabilité corticale chez les adolescents. Ces résultats soulignent a nouveau la différence de sensibilite des adolescents à la lumière.

Cette thèse a exploré les circuits cérébraux impliqués qui permettent a la lumière d'affecter les fonctions cognitives. Elle souligne l'importance de facteurs tels que le moment de la journée et l'âge et contribue a une meilleure compréhension des mécanismes par lesquels la lumière influence les processus cognitifs ce qui pourrait contribuer a la mise au point de solutions d'éclairage intégratif qui favoriseront la santé et le bien-être.

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Abbreviations

AD	Alzheimer's Disease
ANTS	Advanced Normalization Tools
AUC	Area Under the Curve
BLH	Blue Light Hazard
BMA	Bayesian Model Averaging
BMR	Bayesian Model Reduction
BOLD	Blood-Oxygen-Level-Dependent
CCT	Correlated Color Temperature
CTT	Compensatory Tracking Task
DCM	Dynamic Causal Modeling
dLGN	Dorsal Lateral Geniculate Nucleus
DoC	Disorder of Consciousness
EEG	Electroencephalography
fMRI	functional Magnetic Resonance Imaging
GABA	y-aminobutyric acid
GLM	General Linear Model
GLMM	Generalized Linear Mixed Models
GRE-EPI	Gradient-Recalled Echo-Planar Imaging
IFJ	Inferior Frontal Junction
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
MB	Mamillary Bodies
MDN	Medial Dorsal Nucleus
MelEDI	Melanopic Equivalent Daytime Illuminance
MFG	Middle Frontal Gyrus
MNI	Montreal Neurological Institute
MP2RAGE	Magnetization-Prepared with 2 RApid Gradient Echoes
mPFC	medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
NIF	Non-Image Forming
OPN	Olivary Pretectal Nuclei
PD	Parkinson's Disease
PEB	Parametric Empirical Bayes
PET	Positron Emission Tomography
pHb	Peri-Habenular
PLR	Pupil Light Reflex
PON	Preoptic Nucleus

Pp	Posterior Probability
PRC	Phase Response Curve
QC	Quality Control
RF	Radio Frequency
RGCS	Retinal Ganglion Cells
RHT	RetinoHypothalamic Tract
ROI	Region of Interest
S-cones	Short Wavelength-Cones
SAD	Seasonal Associative Disorder
SC	Superior Colliculus
SCN	Suprachiasmatic Nucleus
SD	Standard Deviations
SFG	Superior Frontal Gyrus
SMG	Supramarginal Gyrus
SPM	Statistical Parametric Mapping
TEP	TMS Evoked Potential
TMN	Tuberomammillary Nucleus
TMS	Transcranial Magnetic Stimulation
vLGN	Ventral Lateral Geniculate Nucleus
VLPO	Ventrolateral Preoptic Nucleus
vmPFC	Ventromedial Prefrontal Cortex
VOI	Volume of Interest
UHF	Ultra-High Field

Main Scientific Contribution

Oral conference presentations as first author

R. Sharifpour, I. Campbell, I. Paparella, E. Beckers, F. Balda Aizpu- rua, N. Mortazavi, A. Berger, P. Talwar , E. Koshmanova, L. Lamalle, S. Sherif, G. Vandewalle. **Non-image forming Effects of Light on the Brain: Teenagers vs. Adults**. (2024). ESRS, Seville, Spain.

R. Sharifpour, I. Campbell, I. Paparella, E. Beckers, F. Balda Aizpu- rua, N. Mortazavi, A. Berger, P. Talwar , E. Koshmanova, L. Lamalle, S. Sherif, G. Vandewalle. **The Influence of Blue Light on Cortical Excitability in Adolescents: TMS-EEG Finding**s. (2024). LIGHTCAP symposium: THE INVISIBLE WORKINGS OF LIGHT, Eindhoven, The Netherlands.

R. Sharifpour, I. Campbell, I. Paparella, E. Beckers, F. Balda Aizpu- rua, N. Mortazavi, A. Berger, P. Talwar , E. Koshmanova, L. Lamalle, S. Sherif, C.Philips, G. Vandewalle. **Modulatory Effects of Melanopic Irradiance on Executive Brain Activity in Late Teenagers and Young Adults**. (2023). SLTBR, Lausanne, Switzerland.

R. Sharifpour, I. Campbell, I. Paparella, E. Beckers, F. Balda Aizpu- rua, N. Mortazavi, A. Berger, P. Talwar , E. Koshmanova, L. Lamalle, S. Sherif, G. Vandewalle. **Impacts of Light on Effective Connectivity Among the Working Memory Regions**. (2022). SLTBR, Manchester, United Kingdom.

Publications as first author

Sharifpour, R., Aizpurua, J. F. B., Campbell, I., Paparella, I., Beckers, E., Mortazavi, N., ... & Vandewalle, G. (2024). **Consistent Regional Hypothalamic Response to Illuminance with Time of Day but not with Developmental Age**. *Under preparation*.

Sharifpour, R., Campbell, I., Paparella, I., Aizpurua, J. F. B., Beckers, E., Mortazavi, N., ... & Vandewalle, G. (2024). **Light Impact on Thalamo-Cortical Connectivity During an Executive Cognitive Task: Effects of Time of Day and Specificities of Teenagers**. *Under preparation.*

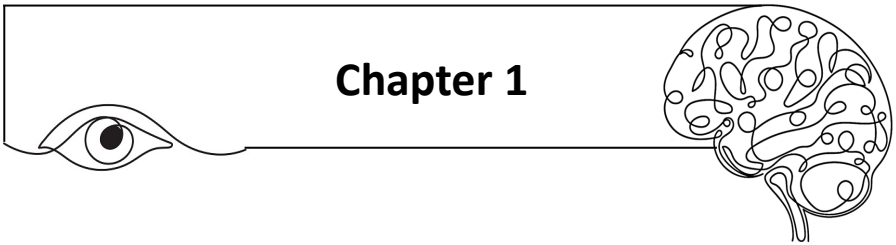
Sharifpour, R., Balda Aizpurua, F., Vandewalle, G. (2024). **Lifetime Changes in the Biological Effects of Light on Non-Visual Brain Functions**. *Under review.*

Sharifpour, R., Balda Aizpurua, F., Paparella, I., Read, J., Leysens, Z., Letot, S., ... & Vandewalle, G. (2024). **Cortical Excitability is Affected by Light Exposure-Distinct Effects in Adolescents and Young Adults**. *bioRxiv*, 2024-08.

Campbell, I.*, Sharifpour, R.*, Aizpurua, J. F. B., Beckers, E., Paparella, I., Berger, A., ... & Vandewalle, G. (2024). **Regional Response to Light Illuminance Across the Human Hypothalamus**. Elife, 13, RP96576.

Preliminary Note: Introduction Structure

This thesis contains two introduction chapters, both of which are essential for providing a comprehensive foundation for the research presented. Chapter 1 offers a broad overview of light as a modulator of NIF brain functions, discussing both the positive and negative impacts of light exposure, as well as factors that can influence these effects. While there is some overlap in content, Chapter 2 builds on the foundation laid in Chapter 1 and narrows its focus to examine how these effects vary across the lifespan, which is central to one of the research objectives of this thesis. I believe that presenting both chapters is necessary to establish the context and theoretical background for the study.



Chapter 1

Introduction I:

Light as a Modulator of Non-Image-Forming Brain Functions: Positive and Negative Impacts of Increasing Light Availability

This chapter is based on our published review paper in Clocks and Sleep:

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. https://doi.org/10.3390/clockssleep5010012

Abstract

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 "non-visual" 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 et al., 2009a). On a longer timescale, light can affect circadian entrainment and influence mood (LeGates et al., 2012; Wirz-Justice et al., 2021).

Light is now emerging as being central to our health and well-being, and several health issues have been associated with unhealthy light environments including sleepiness, cognitive impairments, mood, and sleep disorders (Boyce, 2022; Wirz-Justice et al., 2021). 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 tunable 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 (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., 2021). Governments worldwide are adopting policies in favor of LED lighting. Lighting industries are even proposing LED-integrative lighting products to improve health, mood, or well-being, often with little solid scientific backing (Houser et al., 2021). 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 the understanding of the NIF impact of light a timely research question.

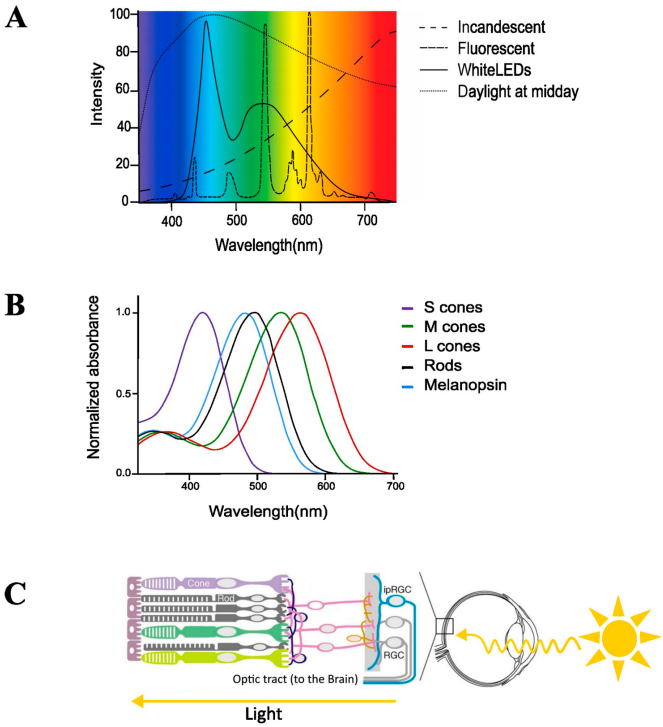


Figure 1-1: Photoreceptor sensitivities and light spectra.
(A) Spectrum of white LED, fluorescent, and incandescent light sources and natural daylight. (B) Spectral sensitivities of retinal photoreceptors in primates. (C) Wiring and position of retinal photoreceptors. ipRGCs: intrinsically photosensitive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

Classical Light-Sensitive Pathways for the Visual System

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 color-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 color 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/m^2) and rod saturation begins at photopic light levels (~10 Cd/m^2). Between scotopic and photopic lies mesoscopic vision with rod and cone contribution to (partially colored) vision (Stockman and 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 and Weller, 1972; 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 et al., 2001, 1999). 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 et al., 1998a).

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 color-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 et al., 1998b). 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., 2009, 2007). 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

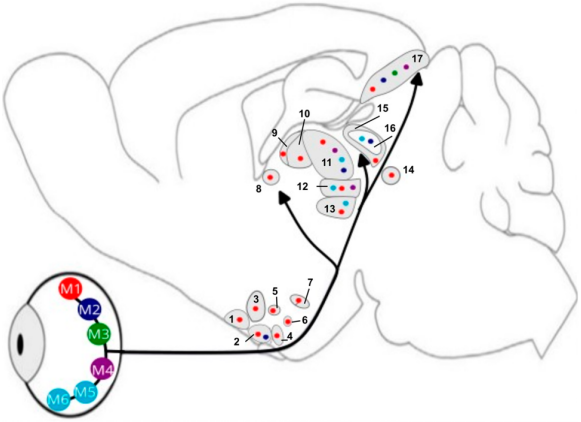
photons most efficient in the 11-cis- to-all-trans switch triggering phototransduction, while the all-trans-to-11-cis reconversion takes place at longer wavelengths, subject to debate (Mure et al., 2009, 2007). Biochemistry investigation reported that chromophore regeneration maximal sensitivity lies 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., 2009, 2007). 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 1012 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., 2012, 2010; 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., 2017, 2015).

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**) (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; Do, 2019). 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 (Do, 2019; Hattar et al., 2006). Information from (Do, 2019; Ecker et al., 2010; Hattar et al., 2006; Zhao et al., 2014). Numbers of the scheme correspond to numbers in the adjacent table. Colored 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 (Huang et al., 2019). Other

non-M1 ipRGC subtypes are known to contribute to visual perception (Sonoda and 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 20s (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 behaviors, 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 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 color discrimination circuit involving M1-ipRGCs. It is proposed that color opponency evolved to distinguish between the different sky colors encountered at different times of the day, to convey timing information to the SCN and to support correct entrainment (Mouland et al., 2019; Rivera and 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 OPN, 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).

Light: Circadian and Acute Impacts

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 (Chang et al., 2011; Hébert et al., 2002). This non-linear change results from the interplay between the circadian system, temporally organizing physiology and behavior, 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 and Eastman, 2009). 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 et al., 2009a). 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-ipRGC suppression (Blume et al., 2022). Light 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 been always consistently shown during the day (Dumont and 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 color 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 favor sleep during light exposure, but they also promote alertness during darkness, i.e., the absence of light is signaled by ipRGCs (Pilorz et al., 2016; Tsai et al., 2009). Translation of the latter finding to humans, where ipRGCs would favor 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 signaling (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).

Beyond the modulation of alertness and sleepiness, light can also acutely improve cognitive performance (Vandewalle et al., 2009a) 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). 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 and 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 (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 signaling are extensively investigated in animal models (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), supraventricular nucleus, and lateral hypothalamus, involved in sleep–wake regulation (Hattar et al., 2006; 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 crossroad between cognition, attention, and alertness (Saalmann et al., 2012), as well as in the LGN (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 (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 et al., 2018, 2011b, 2010, 2007a, 2007b). 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 et al., 2009a). 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 et al., 2016a, 2016b). 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, 2007b). 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 et al., 2011b). 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 et al., 2009b).

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 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 and Santhi, 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-millimeter scale (0.02–1 mm) and inferences about microscopic properties (<0.02 mm; e.g., myelin content and neurite density) (Edwards et al., 2018; 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, it shows that SCN activity is increased during light exposure, in contrast to the 7T MRI study (Sharifpour et al., 2022a). Future research will therefore have to segregate the response of the numerous light-sensitive nuclei of the hypothalamus in humans.

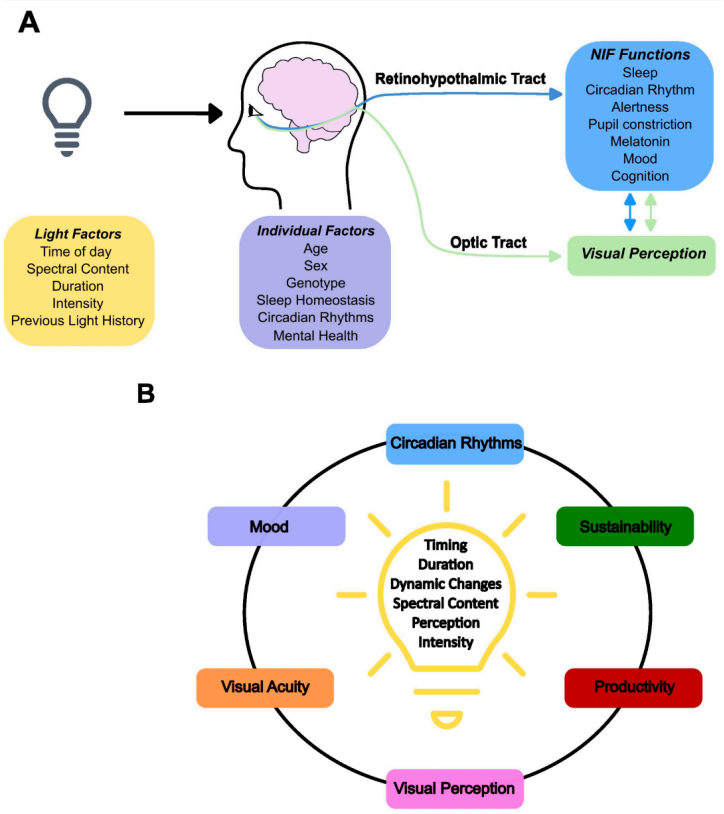


Figure 1-3 Light's impact image forming (IF) and non-image forming (NIF) pathways.
(A) Light signal reaches the central nervous system via the retinohypothalamic and optic tracts of the optic nerve to affect IF and NIF functions. Light impact on NIF functions depends on light factors and individual factors. (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 color-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 keeping relatively constant the stimulation of the other photoreceptors (S.-M. Hung 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 (S.-M. Hung 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 behavioral 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. 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 (Giménez et al., 2017; 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., 2022), 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 and Terman, 2005). Seasonal associative 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 and 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 et al., 2011b). 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 and 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 24 h (Czeisler et al., 1999), morning light is needed to advance the clock and favor 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 well-being is currently under investigation (Kawasaki et al., 2020).

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 and Terman, 2005), which may favor 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 behavioral traits seen in wild-type animals exposed to aberrant light in the evening (LeGates et al., 2012).

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 and 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 (Huang et al., 2021). 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. 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 anti-depressant 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 dorso-lateral PFC, which have opposite activities, in depression (Koenigs and 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, 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 (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 et al., 2022) 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., 2021; 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., 2021). 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, favors 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)).

Health and Lighting

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 and Vos, 2016). 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 BLH 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 (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 (International Commission on Non-Ionizing Radiation Protection (ICNIRP), 2020; Zhou et al., 2018). Studies assessing LED screen devices and low-energy light bulbs have found no evidence of the blue-light hazard exposure limits (Bullough et al., 2019; Lucas et al., 2014).

The position of the Commission Internationale de l'Eclairage is that there is no risk of damage to the retina from the BLH 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 Board of Administration, 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 Board of Administration, 2019), and there is evidence that blue light transmission through the lens changes with advanced age (Daneault et al., 2018, 2014). 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., 2020, 2018). 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 and 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 facts involved in myopia development (Xiang and 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 (Liu et al., 2022). However, the exact impact of screen-emitted light on visual acuity still needs to be thoroughly assessed (Singh et al., 2021). 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 (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 and 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 well-being 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 well-being, research still needs to establish how to optimize the prevention of the negative impacts of inappropriate light while maintaining visual functions and favoring positive NIF effects.

Light Environments

Studies are increasingly looking at how altering light environments in the "real world" may improve health and well-being. 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). Like- wise, 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 improve 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, 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 well-being (**Figure 1-3 B**) (Houser et al., 2021; 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; Giménez et al., 2017). 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., 2021).

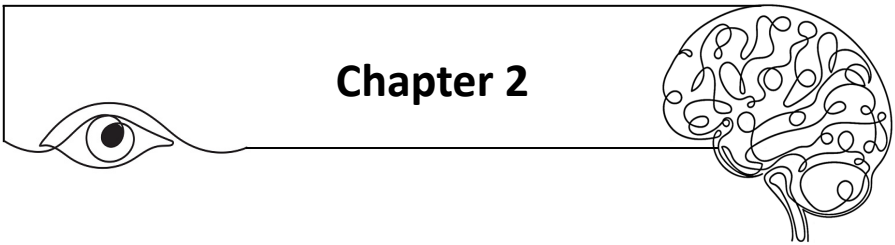
Finally, as we continue to develop lighting environments that ”mimic” natural daylight, more evidence is required to understand the assumed benefits of natural daylight over electrical lighting (Wirz-Justice et al., 2021). A full discussion on natural daylight is beyond the scope of this review; however, it is important to recognize the importance of natural daylight for human health and well-being. 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 well-being.

Conclusions

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 characterized. 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 inter- individual 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.



Chapter 2

Introduction II:

Lifetime Changes in the Biological Effects of Light on Non-Visual Brain Functions

This chapter is based on our review paper that is under review:

Balda, F., Vandewalle, G., & **Sharifpour, R**. (2024). Lifetime changes in the biological effects of light on non-visual brain functions. Neuroscience and Biobehavioral Reviews.

Abstract

Biological effects of light go beyond vision and influence non-image forming (NIF) brain functions such as sleep, circadian regulation, mood and cognition. These effects are primarily driven by the third class of photoreceptors (called ipRGCs), which are maximally sensitive to blue wavelength light and confer a maximal effectiveness of shorter wavelength light on NIF functions. Despite the growing recognition of the importance of light's NIF effects, most research has focused on young, healthy adults, while the impact of light may change during the early development and aging of the brain. This narrative review describes how the NIF effects of light change across the lifespan from fetal development and childhood (when data is available) through adolescence, adulthood and into older age. We begin by discussing how age impacts ocular structure, particularly the changes in photoreceptors. The discussion then shifts to the broader NIF effects of light on brain function and cognition, examining how light influences various cognitive processes, including memory, attention, and emotional regulation, across the lifespan. Finally, we assess how age alters key physiological responses to light, such as pupil light reflex, melatonin production, and circadian entrainment, highlighting differences between children, teens, and the elderly. In the final section, we propose a figure that attempts to summarizes all the main findings we reviewed. Our review underscores the complexity of light's impact on the brain across the lifespan and, most often, the insufficient amount of data to draw firm conclusions, particularly at younger ages. More research is warranted to truly build upon the promises of the effectiveness of individualized light interventions to optimize brain function.

Introduction

Light does not only allow vision, but it is also an essential cue for many biological functions that are not directly related to vision. These functions of light are often referred to as non-visual or non-image-forming (NIF) (Campbell et al., 2023). Exposure to light is the main time giver or *zeitgeber* of the circadian system which organizes physiology in time over the 24h rest-activity cycle (Duffy et al., 1996) . Light therapy for a few weeks can improve affective state and treat mood disorders (Glickman et al., 2006; Westrin and Lam, 2007). Light exposure can also trigger acute effects on physiology, including on cognition, alertness and sleep (Brown et al., 2022; Campbell et al., 2023; Lok et al., 2018). As modern life mostly takes place indoors, artificial lighting is most often governing the impact of light on our physiology. The consequences of this artificial situation are non-trivial since the content in blue wavelength light, which is the most efficient in driving NIF

effects, is most often distinct between artificial and natural light. Inappropriate lighting can indeed lead to negative impacts on well-being and health, including cognitive deficit, daytime sleepiness, poor sleep and mood (Brown et al., 2022; Campbell et al., 2023). Consequently, acting on light stands a promising means to improve brain function and reduce for instance daytime sleepiness and cognitive deficits (Brown, 2020; Didikoglu et al., 2023; Gooley et al., 2011; Münch et al., 2017; Riemersma-van der Lek, 2008; Scheuermaier et al., 2018; Wirz-Justice and Benedetti, 2020).

These interventions will require a detailed understanding of the effects of light on brain function, and the variability in these effects. Most of our knowledge of the impact of light on the human brain is based on young and healthy adults. However, brain maturation, aging, and degeneration all affect brain function. In addition, changes in the eye may modify the light input to the brain. In this narrative review, we focus on the known changes in the impacts of light that may occur across the healthy lifespan. We will only consider aspects of brain functions that have received, in our view, enough attention to allow tentative conclusions: cognitive brain function, pupil light reflex, melatonin suppression and circadian entrainment. In each section we will provide an overall view of the biology of the NIF impacts of light in young adults before detailing the current understanding of the changes taking place from infancy to older age. In the final section, we provide a figure that attempts to summarizes all the main findings we review in a single display.

NIF Photosensitivity through the Eye

NIF signaling of light in the retina is mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs), which make up ~5% of retinal ganglion cells (RGCs) in animals and ~1% in humans (Do, 2019; Lucas et al., 2014; Mure, 2021). These cells express the photopigment melanopsin, with maximal sensitivity around 480 nm, and combine their intrinsic photosensitivity with input from rods and cones to shape their response to light (Do, 2019). Although ipRGCs can effectively signal the capture of single photons, their scarcity makes them less sensitive to light compared to rods (Do, 2019). While rods respond to very low light levels, ipRGCs require a higher photon flux to respond, though still lower than that required by cones (Do, 2019). Additionally, ipRGCs have relatively slow response dynamics, taking up to a few seconds at low light levels and a few hundred milliseconds at higher levels (Berson et al., 2002). In contrast to rods and cones, ipRGCs continue firing even after light extinction, influencing pupil size during subsequent darkness (Adhikari et al., 2015). This persistent response depends, however, also on inputs from rods and cones (Kostic et al., 2016). In contrast to rhodopsin and cone opsins, the melanopsin photopigment consist of

bistable form, with the *trans* form mediating phototransduction – with maximal efficiency under short wavelength light, and photoisomerization to the 11-cis state – potentially with maximal efficiency under long wavelength red light, though it is still debated (Mure et al., 2009, 2007; Sexton et al., 2012b).

Up to six classes of ipRGCs have been identified in animals, each with distinct morphology, dendrite location, response dynamics, and brain projections (Schmidt et al., 2011). A full understanding of the diversity of ipRGC types and of their responses is still lacking, especially in humans. Although not the main focus here, it is important to note that ipRGCs also contribute to basic visual functions. They are involved in brightness perception, regulating the sensitivity of rods and cones, and contribute to coarse image formation, including in humans(Allen et al., 2019; Brown et al., 2012; Ecker et al., 2010).

We can intuit the retina undergoes profound modifications over the lifespan. Maturation of cones' outer segments, including over the fovea, was reported to be continuous during childhood and adolescence possibly through cone migration, which thickens the outer layer of the retina (e.g. by age 15 months, cones' outer segment is half the length of adults, by age 45 months it is still not the size of adults) (Yuodelis and Hendrickson, 1986). The literature on changes in cone density is inconsistent. While some studies have reported no change in cone density (Curcio et al., 1993; Mirhajianmoghadam et al., 2020), others covering a wide age range, have documented a decreased cone density with aging (Panda-Jonas et al., 1995; Song et al., 2011), such that cone density for a 37-year-old is reported to be twice that of a 45-month-old child (Yuodelis and Hendrickson, 1986). Annual cone loss has been estimated to be between 0.2% and 0.4% (Panda-Jonas et al., 1995) or 104-116 cells/mm^2 (Tumahai et al., 2018). It has been suggested that cone density loss is not consistent throughout the lifespan but rather occurs in two phases: an initial plateau followed by a subsequent decline (Tumahai et al., 2018). There are also studies showing considerable resistance of cones with aging and many structural changes, like the shortening of the outer segments (Curcio, 2001; Elsner et al., 2020).

With aging, we can also observe a notable decline in rod photoreceptors, especially within the macula. With aging, the number of rods in the macula may diminish by up to 30%, with the most pronounced decline happening in the parafoveal area, 1-3 mm from the fovea. This reduction can lead to decreased scotopic sensitivity and a deterioration in rod function, including slower dark adaptation, which extends by about 8 seconds per decade in adulthood (Curcio et al., 2000). Likewise, photopic sensitivity is affected in several ways with aging, like decline in photon

absorption rate, color acuity, contrast sensitivity and flicker sensitivity (Bi et al., 2016; Braham chaouche et al., 2021; Yokoyama et al., 2021).

Animal studies further showed that ipRGCs are photosensitive in newborn and early postnatal mice, before the development of rods and cones (Hannibal and Fahrenkrug, 2004; Schmidt et al., 2008). One study indicates that NIF functions in early neonatal mice are exclusively mediated by ipRGCs. As the eyes open and rods and cones develop, ipRGCs begin to integrate signals from these photoreceptors, resulting in a larger and faster onset of ipRGC depolarization, quicker offset, increased sensitivity, and a slight shift in peak sensitivity from 480 nm to 490 nm (Schmidt et al., 2008).

A postmortem study reported that the structural integrity of ipRGCs remains relatively constant until the age of 50 (Esquiva et al., 2017). Beyond the age of 70, the complexity and density of ipRGCs begin to exhibit significant declines. The number of ipRGCs can fall by up to 44% compared to younger retinas and by 31% compared to those of 30-50 year-old donors. Additionally, dendritic complexity decreases markedly, especially when comparing individuals aged 50-70 to those over 70, as well as the dendritic profiles of M1 cells from 10 and 80 year-old retinas (Esquiva et al., 2017). These observations appear consistent with animal studies where significant decline in ipRGCs occurs only in advanced aging stages (Semo et al., 2003) while evidence gathered across species also estimated 35-40% decline in all-type RGCs over the adult lifespan (Neufeld and Gachie, 2003).

IpRGC loss or reduced arborization may result in a reduce photosensitivity as suggested, for instance, in an elderly donor (over 70) (Esquiva et al., 2017). Several studies suggest, however, the development of compensatory mechanisms to increase the sensitivity and firing rate of ipRGCs (Semo et al., 2016). The relatively late commencement of notable alterations in ipRGCs supports a high resistance of ipRGCs to injury and to aging with respect to other RGCs, possibly because of the expansive dendritic fields of ipRGCs (Li et al., 2006; Robinson and Madison, 2004). The loss of intrinsically photosensitive retinal ganglion cells (ipRGCs) and alteration in their morphology — including altered dendritic arborization, smaller cell bodies, and a patchier distribution of melanopsin— appears to accelerate in certain neurodegenerative conditions, such as Alzheimer's and Parkinson's diseases (AD and PD) (La Morgia et al., 2016; Ortuño-Lizarán et al., 2018). IpRGCs may, however, be resistant to RGC neurodegeneration in Leber's Hereditary Optic Neuropathy which has been used as human models to investigate the NIF effects of light (Evangelisti et al., 2021; La Morgia et al., 2010; Romagnoli et al., 2023). Besides photoreceptor changes, pupil size decreases due to senile miosis, with some authors reporting a linear reduction of 0.015 to 0.043

mm per year, because of factors like sphincter muscle atrophy, iridial rigidity, altered autonomic tone, and chronic fatigue (Winn et al., 1994). The accumulation of crystalline aggregates and yellow chromophores in the lens, commonly known as "lens yellowing," also accompany aging. This process causes increased lens density and reduces light transmission, particularly for blue light, and results in a relative "blue blindness" in older individuals. Attempts to quantify this reduction reveal significant decreases in transmittance: transmittance for short-wavelength light would be reduced by 53% between 20- 35y young adults and 55-70y older people, and by 45% between 36-55y middle-aged and older people. For long-wavelength light, there would be a 17% decreased transmittance between 20- 35y young adults and 55-70y older people, and a 5% decrease between 36-55y middle-aged and 55-70y older people (Najjar et al., 2016). However, whether lens yellowing and senile miosis affect the NIF biological impacts of light or whether compensatory mechanisms take place remains debated (see below). IpRGCs may indeed be able enhance their sensitivity to offset the reduced photon absorption caused by lens yellowing, such as increasing the presence of the 11-cis form of melanopsin (Najjar et al., 2014; Sexton et al., 2012a).

Projections of IpRGCs to the Brain

Due to methodological limitations in human research, the brain pathways of ipRGCs have been largely studied in animal models (Do, 2019). IpRGCs innervate 70% of approximately 46 RGCs' brain targets (Lawrence and Studholme, 2014). These projections encompass areas related to both image-forming and non-image-forming functions. Broadly classifying the target regions based on their roles in physiology and behavior, we can categorize the main projections in 7 groups:

1- Circadian Entrainment

The suprachiasmatic nucleus (SCN) is a primary target for ipRGCs and receives dense direct inputs from these cells via the retinohypothalamic tract (RHT). The projections to the SCN mainly come from the M1 subtype of ipRGCs and, with a lesser contribution, from the M2 subtype (Fernandez et al., 2016). IpRGCs also reach the thalamus in intergeniculate leaflet (IGL) which is a necessary nucleus for circadian entrainment since it sends inputs to the SCN. This nucleus receives its projections mainly from M1 and M6 (Berry et al., 2023; Quattrochi et al., 2019). The IGL is considered to correspond to the pregeniculate nucleus of the thalamus in primates including humans. As in rodents, the pregeniculate nucleus projects to the SCN (Moore, 1989).

2- Sleep-Wake Regulation

IpRGCs project to various hypothalamic nuclei, not limited to the SCN, including the ventrolateral preoptic nucleus (VLPO) and lateral hypothalamus (LH) (Costa et al., 1999; Ecker et al., 2010; Hattar et al., 2006; Lawrence and Studholme, 2014) that both play a key role in sleep-wake regulation (Zhang et al., 2021). These two regions receive their inputs from M1 ipRGCs (Aranda and Schmidt, 2021).

3- Pupillary Light Reflex

The olivary pretectal nucleus (OPN), located in the midbrain, is another target for ipRGCs. OPN shell (sOPN) plays a crucial role in the pupillary light reflex (PLR) pathway (Aranda and Schmidt, 2021). It has been shown that M1 ipRGCs are the subtype that extensively project to the shell of the OPN while avoiding the core (Baver et al., 2008; Hattar et al., 2006).

4- Mood

Light can influence brain areas associated with mood regulation either directly or indirectly through pathways that pass through the SCN, ventral lateral geniculate nucleus (vLGN), and IGL. M1 ipRGCs directly project to the amygdala (medial amygdaloid nucleus) and perihabenular nucleus (PHb) of the thalamus (Huang et al., 2019). Indirect pathways involve the ventral tegmental and raphe areas receiving innervation from the SCN, as well as the lateral habenula (LHb) being innervated by the vLGN and IGL that receive input from M4 ipRGCs (Milosavljevic, 2019).

5- Attention/Alertness

Projections of ipRGCs go to the brainstem in the superior colliculus (SC),that is involved in attention and eye movement coordination (Lyon et al., 2010), as well as the pulvinar, a central hub in the thalamus interconnecting cognition, attention, and alertness (Saalmann et al., 2012).

6- Memory and Learning

The hippocampus, a key area associated with learning and memory, indirectly receives light signals from ipRGCs through the SCN (Vidal-Villegas et al., 2021). Human fMRI studies have also reported increased activation in brain regions like the hippocampus and insular regions in response to short-wavelength light, indicating a potential pathway to these areas (Vandewalle et al., 2009a).

7- Vision

As previously mentioned, ipRGCs contribute to image forming functions through their projections to visual processing areas, including the dLGN and visual layers of SC. These projections mainly come from non-M1 subtypes (Brown et al., 2010; Ecker et al., 2010; Hattar et al., 2006).

The majority of these projections were uncovered in nocturnal laboratory animals. Translation to diurnal humans, where the later maturation of the cortex allows for complex cognitive processing (Braak and Del Tredici, 2015), remains limited. However, there are notable exceptions. In both diurnal rodents and non-human primates, ipRGC projections have been reported to several key regions. These include the SCN, IGL (pregeniculate nucleus in primates), OPN, LGN, and SC (Dacey et al., 2004; Hannibal et al., 2014; Langel et al., 2015; Ruan et al., 2006). While it seems that a diurnal rodent had overall similar ipRGCs projections, specificities were reported. Specifically, the vLGN, dLGN and the OPN receive less innervation from ipRGCs in grass rats compared to reports in nocturnal rodents (Langel et al., 2015).

All the structures mentioned above undergo changes over the lifespan and covering them goes beyond the scope of this review. Research on age-related changes in ipRGCs projections, their density for instance, is almost inexistent. One notable exception is the fact that ipRGCs present functional connections with the suprachiasmatic nucleus at birth, implying that the NIF pathways become functional much earlier in development than the image-forming pathways (Sekaran et al., 2005). When ipRGCs projections to other brain targets take place during development is not known.

Impact of Light on Cognitive Brain Function

The impact of light on cognitive brain function is directly related to the functions of the targets of ipRGCs listed in the preceding section (we will not cover vision in this review). The functional impact of ipRGCs on their direct anatomical projections has been predominantly investigated in nocturnal rodents. A seminal paper used conditional activation of ipRGCs and reported evoked circadian phase resetting and pupil constriction as well as c-Fos induction – a marker of neural activation – in almost all the areas mentioned in the previous section, including multiple nuclei in the hypothalamus, thalamus, and limbic system (Milosavljevic et al., 2016). As an example, we highlight the densest, and probably most documented, projections of ipRGCs to the SCN, site of the principal circadian clock, emphasizing the key role of ipRGCs in circadian entrainment and regulation of sleep and wakefulness (Altimus et al., 2008). The SCN shows increased c-Fos expression in response to light. The effect in nocturnal rodents is phase dependent, with light

increasing c-Fos expression at night/dark phase and having less or little effect during daytime/light phase (Krajnak et al., 1997). It also appears that it is through the projection of ipRGCs to the SCN that light affects learning (Fernandez et al., 2018); an observation that is in line with the need for a functional SCN for hippocampus-dependent learning (Fernandez et al., 2014; Ruby et al., 2008). As another example and still in rodents, ipRGCs projecting to the central and medial nuclei of the amygdala are reported to mediate at least part of anxiety-related behaviors following acute light exposure, likely totally independent of the SCN (Vinkers et al., 2010; Wang et al., 2023). These findings highlight the diverse and intricate role of ipRGCs' projections in modulating various behaviors in rodents.

The investigation of the NIF impact of light beyond the initial synapses of ipRGCs remains scarce in rodents. A notable exception, however, is the involvement of ipRGCs in controlling the activity of the ventromedial prefrontal cortex (vmPFC), a crucial region for regulating emotional and social behaviors. This regulatory function, which operates independently of circadian and mood changes, is facilitated through an ipRGC-thalamic-corticolimbic pathway (Ospri et al., 2024) . In addition, the impact of light on mood-related measures was associated with ipRGCs' projections to the perihabenular nucleus of thalamus (PHb), a key region of the regulation of affective state, that would in turns pass on light signal to the nucleus accumbens or to the vmPFC (Fernandez et al., 2018).

While focusing on small areas/nuclei of the brain is difficult in humans, neuroimaging techniques applied to humans provide the advantage of collecting data over the entire brain. Several studies reported light-induced increases in activity in cortical regions involved in the ongoing cognitive processes (attentional, executive, emotional domains), both at night and during the day (Campbell et al., 2023). Light increased the activity within the prefrontal and parietal cortices during auditory task, in areas involved in executive and attentional processes (Alkozei et al., 2016a; Vandewalle et al., 2007a, 2006). Areas of other cortices, within the insular, occipital or temporal lobes were also affected by light depending on the ongoing task (Vandewalle et al., 2011b, 2007a, 2007b, 2006)(Vandewalle et al., 2011, 2007a, 2007b, 2006). Light may also enhance the activity in the anterior cingulate cortex in an emotional context related to anticipation and decision-making (Alkozei et al., 2016a). All these modulations were detected comparing polychromatic white light to darkness or blue monochromatic light to other monochromatic longer wavelength light, suggesting that ipRGCs were driving at least part of the effect. Additional support for a role of ipRGCs comes from an investigation in visually blind individuals with intact non-image-forming photoreception (and very likely ipRGC), which showed increased brain responses to auditory tasks

while exposed to blue light (Vandewalle et al., 2013; Zaidi et al., 2007) (Vandewalle et al., 2013; Zaidi et al., 2007) and from a study showing that manipulating light history triggered change in the impact of light that could be explained through a theoretical change in ipRGCs' sensitivity (Chellappa et al., 2014). The effects of light on cognitive brain responses were further found to vary depending on circadian phases and sleep homeostasis, with light impact relatively lower in the evening and relatively larger following sleep deprivation (Vandewalle et al., 2011b).

When using light exposure lasting <1min, significant changes tended to be more present over subcortical areas rather than in the cortex, suggesting that the impact of light on NIF function was mediated by subcortical structures (Vandewalle et al., 2007b). The thalamus, in an area compatible with the pulvinar, seems to be among the areas and may act as a relay between the subcortical structures involved in alertness regulation and the cortex (Paparella et al., 2023; Vandewalle et al., 2006). The only positron emission tomography (PET) study that focused on the NIF impact of light found that during the biological night, exposure to light decreased the activity of the anterior hypothalamus in an area encompassing notably the SCN during the darkness period immediately following the exposure (Perrin et al., 2004). This early observation was recently confirmed by 2 fMRI investigations, which used high-resolution 7 Tesla MRI (Campbell et al., 2024b; Schoonderwoerd et al., 2022). Interestingly, a concomitant increase in activity was also found over the posterior part of the hypothalamus suggesting an anterior-posterior gradient in the functional impact of light on the hypothalamus (Campbell et al., 2024b). Hypothalamus nuclei, such as the lateral hypothalamus or the SCN are therefore likely receiving ipRGC signaling and mediating in part the impact of light on NIF brain functions, possibly through a relay in the pulvinar. Another relay may be found in the locus coeruleus (LC) in the brainstem which may be affected by light onset in fMRI study involved an executive task, though the resolution of the 3T MRI apparatus only allows speculative localization (Vandewalle et al., 2007a). Indirect support for an involvement of the LC was recently gained through analyses of transient changes in pupil size in responses to auditory stimulations warranting further high-resolution imaging focused on the LC (Campbell et al., 2024a).

The impact of light on emotional responses may act via a brain pathway in part different from attention, executive functions and alertness. While the posterior and anterior hypothalamus are affected by light in an emotional context , light is likely influencing activity in the amygdala, though both increased or decreased activity were reported (McGlashan et al., 2021; Vandewalle et al., 2010), potentially because of insufficient resolution (using 3T MRI) to distinguish different responses across amygdala nuclei (some of which receive ipRGCs' projections). In addition to

studies that used fMRI and PET imaging to evaluate the influence of light on brain regional activity, several studies, that we don't cover in detail, used electroencephalography (EEG) to look at the impacts of light on brain signal patterns. It has been reported that EEG correlates of alertness are more affected by blue short-wavelength light than longer-wavelength light (Cajochen et al., 2005; Chellappa et al., 2013; Lockley et al., 2006; Santhi et al., 2012). Another study used EEG on blind individuals and reported increased alpha power over the occipital cortex, suggesting awareness of monochromatic blue light in blind individuals (Vandewalle et al., 2018). A more in-depth review of how light can affect many aspects of human brain function when assessed in vivo through neuroimaging can be found elsewhere (Campbell et al., 2023; Lok et al., 2018).

No PET or fMRI studies have been conducted on pre-adult populations - infant, children or teenagers – such that the changes occurring over this lifetime period are not very well known. There is, however, research indirectly related to brain functions and light in the youngest. Infants aged 6-12 weeks who experienced higher light intensity in the early afternoon had more consolidated sleep at night (Harrison, 2004). In children aged 3-6 years, later and shorter light exposures were linked to later sleep onset and sleep offset (Ulset et al., 2021). Few studies investigated the impact of room light on cognitive outcomes between ages 4 and 12 years and reported mixed findings. Some of them found that higher correlated color temperature (CCT) lighting, which measures the color appearance of light, was beneficial for concentration and on-task behavior (Hviid et al., 2020; Pulay et al., 2018; Sleegers et al., 2013), while others did not find such association or at least not an overall improvement in cognitive tests (Hartstein et al., 2018; Mott et al., 2012). Reduced outdoor light exposure during winter was associated with increased sadness in 2-year-old children (as reported by their teachers), while frustration, aggression, and activity levels remained unchanged (Ciucci et al., 2011). Conversely, no correlation between daily light exposure and crying in infants aged 6-12 weeks (Harrison, 2004) and no significant link between light exposure and positive/negative effects was found in children aged 3-6 years (Lagacé-Séguin and d'Entremont, 2005). Overall, research on the impact of light on children's emotions has yielded mixed results. More details regarding studies in children can be found in a recent review (Westwood et al., 2023).

Students aged 16-19y were found to exhibit faster cognitive processing speed and improved concentration under blue-enriched white lighting compared to standard lighting. However, this lighting did not affect short-term memory encoding and retrieval, suggesting its impact is mainly on basic information processing (Keis et al., 2014). Inconsistencies in exposure periods, testing protocols, and mixed evidence limit the comparability with findings in adults. A significant

association between duration time of bright light therapy (BLT) device use and increased beta power in frontal area was uncovered as well as improvements in math performance and attention test (Teicher et al., 2023). Although it is reasonable to assume that children and adolescents may exhibit different sensitivities to light stimuli (cf. previous sections), none of these studies directly compared these youngest age groups with adults.

There is, in contrast, more insight available at the other end of a lifetime. Similarly to young adults, exposure to blue light was found to increase cortical and thalamus cognitive activity in healthy older individuals aged > 55 (Daneault et al., 2014). Yet, compared to younger adults, older participants were less affected by light in several brain regions including the pulvinar, part of the prefrontal cortex, as well as possibly in ventral tegmental area (VTA), which is an important source of dopamine. These findings were later confirmed, and it was found that the reduced impact of light on cognitive brain activity (still using auditory tasks) was not solely explained by senile myosis or lens yellowing, as controlling for pupil size and including individual with novel lenses following cataract surgery did not abolish age-relate differences (Daneault et al., 2018). This latter finding may arise in part from the relatively long gap between lens replacement and brain measurement (~4-years). A study investigating light impact on diverse physiological responses to light closer to cataract surgery (~4-8-weeks) found improvement in several responses to light including in sleep and cognitive function. The brain may therefore adapt to the gradual ocular changes associated with aging, as well as to lens replacement. Reduced impact of monochromatic blue light in aging has been reported for some acute responses such as subjective alertness, sleepiness and mood (Sletten et al., 2009) (Sletten et al., 2009). In another study, polychromatic light conditions from non-blue enriched light (2500K) to blue-enriched light (6500K) at low light levels (as in typical indoor settings) were used to assess the link between aging and light sensitivity. While young adults showed increased melatonin suppression and improved subjective sleepiness and psychomotor vigilance task (PVT) performance under 6500K, older individuals did not show any difference in those indices across light conditions (Chellappa et al., 2021). This reduced sensitivity to light may suggest that light exposure may have to be stronger as we age to reach the same level of stimulation of cognitive brain functions.

Pupil, Melatonin, Circadian Entrainment in Aging

Pupillary Light Reflex and Post-Illumination Pupil Response

Focusing on the pupil provides an easy read-out of the impact of light on brain function. It is therefore not surprising that it has received a substantial scientific interest with respect to lifetime changes in the impact of light. Although the impact of light on pupil size depends on input from all retinal photoreceptors, the overall picture is that rods and cones mainly contribute to the acute pupil constriction (<~10s) while ipRGCs intrinsic sensitivity is responsible for the sustained pupil constriction over longer exposure (McDougal and Gamlin, 2010). IpRGCs also trigger a lasting relative pupil constriction after light exposure, known as the post-illumination pupil response (PIPR). This response consists of a partial constriction of the pupil following its dilation at light off, most likely because of the continued firing of ipRGCs (Kankipati et al., 2010). Evidence from studies on newborns and children up to two years of age suggests that pupil size begins to increase during the early stages of life, with this growth trend continuing into adolescence, when the pupil reaches its peak size (Ikeda et al., 2015; Kercher et al., 2020; MacLachlan and Howland, 2002). Furthermore, 38-week gestational infants already demonstrate a pupillary light reflex (PLR) in response to blue light, but not red light, indicating that PLR at these early stages of development may be primarily mediated by ipRGCs (Ikeda et al., 2015). The involvement of rods and cones likely develops later. Additionally, PLR measures, such as pupil constriction, increase between 6 and 24 months (Kercher et al., 2020), while PLR latency decreases from 6 months to 9 years (Daluwatte et al., 2013; Dinalankara et al., 2017). It has also been observed that the PIPR in individuals aged 5 to 15 years is qualitatively similar to that of adults (Ostrin, 2018). However, when comparing participants aged 16 to 35 years, aging was associated with a reduction in PIPR (Van Der Meijden et al., 2016). In this latter study, PIPR strength was further found to be associated with larger delay of sleep timing, suggesting that ipRGC intrinsic sensitivity was related to sleep timing in that age range (Van Der Meijden et al., 2016).

The literature suggests that pupil light sensitivity may decline with age during later adulthood, though the findings are sometimes contradictory. A correlation between age and reduction in the sustained constriction during the light exposure was reported in participants between 26 and 68 years (Herbst et al., 2012). PLR was, however, not different between healthy older individuals aged 50 to 70 and younger individuals aged 18-30y in several studies (Daneault et al., 2012). Although these studies led to different conclusion – potentially because of differences in the age of the recorded participants and in the variety of light condition administered (monochromatic blue, green, red and polychromatic light) – they both reported that the older participants consistently exhibited smaller pupil sizes across all light conditions, particularly at low irradiances ($7x10^{12}$

photons/cm^2/s). A positive correlation between PIPR and baseline pupil size was detected in a sample of 19-80 years old participants, but no significant relationship between PIPR and aging was found (Kankipati et al., 2010). In contrast, the early part of the early postimulus area under the curve (AUC) (Herbst et al., 2012) following blue light exposure was reported to be increased in older individuals and the findings were not accounted by rod- or cone-induced rapid redilation after light off, potentially implying an alteration in ipRGC intrinsic response. Interestingly also, decreased lens transmission was associated with reduced early PIPR, although lens transmissions - which is correlated with age – appeared less associated than age itself. Overall, while PLR may or may not be reduced in aging, it seems that PIPR, mainly driven by ipRGCs, is altered in aging though it may be due to the decrease in lens transmittance.

Melatonin Secretion

Light suppresses melatonin secretion by the pineal gland - in the evening/at night, i.e. when it is produced, and it is the aspect probably most commonly considered to investigate the NIF biological impacts of light. This is likely because melatonin metabolites can be routinely assayed in the saliva, such that, as for the pupil, it is a relatively accessible parameter of an important NIF function of the brain.

Children were found to be more sensitive to light-induced melatonin suppression than adults. For example, in preschoolers aged 3 to 5, even low-intensity light exposure before bedtime can reduce melatonin production by up to 70% and provoke sustained melatonin suppression after light offset (Hartstein et al., 2022). In older children, such as those aged 8 to 10, melatonin suppression can be up to twice as large as in adults (Higuchi et al., 2014). This heightened sensitivity is likely due to children's larger pupils and clearer lenses, which allow more light to enter their eyes. The sensitivity to light seems to decrease afterwards and there is a report that melatonin suppression is reduced between early and mid-puberty teenagers (Crowley et al., 2015), even though adolescents still show higher melatonin suppression than adults (Höhn et al., 2024; R. Nagare et al., 2019; R Nagare et al., 2019). This could mean that evening light could be especially disruptive for children and teenager sleep, which may be a problem considering the increasing presence of artificial light through portable screen devices (Chellappa, 2021). Using blue blocking lenses in the evening may provide a response to this issue. It was reported that the use of such blue blocking lenses for one week in the evening decreased melatonin suppression in teenagers while it increased and decreased subjective sleepiness and alertness respectively (while objective measures related to sleep did not change) (Van Der Lely et al., 2015). Importantly, however,

melatonin secretion in teenagers may recover faster, i.e. return to normal dim light level quicker than adults following an exposure, suggesting that the disruptive effect of light on circadian rhythm (and sleep) may be reduced in teenagers and warranting further research (Höhn et al., 2024).

Several studies reported that, as adults get older, they undergo less melatonin suppression when exposed to light in comparison to their younger counterparts especially when they are exposed to short wavelength light, suggesting lens yellowing as the underlying cause (Chellappa et al., 2021a; Ferrari et al., 2000; Herljevic et al., 2005; Iguchi et al., 1982; Waldhauser et al., 1988). One study found, however, no strong dose-response relationship between melatonin suppression and illuminance (Duffy et al., 2007). A shift in the peak sensitivity of melatonin suppression, again possibly due to lens yellowing, may also take place and melatonin suppression would in fact remain unchanged once assessed at its peak sensitivity (Najjar et al., 2014). It should be noted that difference in melatonin suppression between young and older adults may only be present for low and intermediate illuminances while suppression saturation under high illuminance, which has been less actively tested, may remain unchanged (Eto and Higuchi, 2023; Zeitzer et al., 2000). Although one study looking at low to moderate levels of illuminance did not find differences in melatonin suppression between teenagers and adults (Duffy et al., 2007), the limited number of studies suggests that more research is needed to draw definitive conclusions.

Circadian Entrainment

The ability of light to shift the clock is critical to adapt to different rest-activity schedule (shift-work, jet-lag) and depends on the timing of the exposure as captured in phase response curve (PRC). In essence, morning light exposure advances the circadian clock while evening and late-night exposures delay it (Blume et al., 2019; Khalsa et al., 2003; Lewy et al., 1992). Although circadian rhythmicity is present in many aspects of brain function, the circadian secretion of melatonin, is almost the only parameter considered when it comes to PRC; and this is also true when it comes to PRC and aging. Yet, the circadian clock changes across the lifespan and its response to light as well.

There is no published PRC in infants or children. On average parents set their children's bedtimes about 48 minutes after melatonin onset (Lebourgeois et al., 2013). There is, however, a large variability which can lead to later bedtime relative to melatonin onset and complicate studies on circadian entrainment and light-induced phase shift in children. A recent study reported that children’s circadian clock (i.e. melatonin secretion) may be shifted by even low levels of evening light (Hartstein et al., 2023). This may contribute to some of the sleep problems found in children,

which seem to peak around preschool. To address these challenges, future longitudinal studies could help account for individual variability

Teenagers tend to become later chronotypes, which may be prone to a phase delay by evening light. A shallower build-up of sleep pressure may push them to stay awake later when light is available, curtailing their already insufficient sleep (Tarokh et al., 2019). This may again constitute an issue as teens are high consumers of screen devices, including in the evening. A PRC compiled in teenagers found, however, that circadian rhythms do not respond differently to light during adolescence as compared to young adults. It seems, however, that the PRC may be symmetrical in teenagers – while in adults the phase advance portion of the PRC is smaller than the phase delay portion (Crowley and Eastman, 2017).

Older adults tend to become earlier chronotypes as they age and, concomitantly, the ability of their circadian clock to accommodate light/dark schedule changes may be impaired (Hood and Amir, 2017; Skene and Swaab, 2003). Several investigations indicate that the shift in the rhythmicity of melatonin secretion might be reduced in aging, both in the phase delay and phase advance portion of the PRC (Benloucif et al., 2006; Sletten et al., 2009). Part of the changes in the impact of light on circadian rhythmicity may come from a change in the position of the sleep episode over the circadian cycle (phase angle between sleep and circadian phase). Older individuals may have their sleep episodes earlier with respect to their melatonin secretion profiles, masking therefore part of the phase delay potion of their PRC and reducing thereby the ability of evening light to phase-delay the circadian cycle (Benloucif et al., 2006). The ability of light to delay the circadian phase was also found to be reduced in older subjects exposed to low-moderate illuminance (50-1000 lux) and they needed higher non-saturating illuminance to experience the same phase shift as the younger group (Duffy et al., 2007).

Conclusion

Recent development switched the indoor lighting from incandescent light bulbs, that were poor in shorter wavelength blue light, to LEDs that are enriched these wavelengths compared to natural light (Campbell et al., 2023). This has profoundly modified the concerns related to light from being depleted in short wavelength light during the day, and particularly in the morning, to being overexposed to blue enriched light, particularly in the evening through the use of portable electronic devices. Several studies investigated how to rebalance individual light exposure profiles (Crowley et al., 2024; Kawasaki et al., 2021; Stevenson et al., 2024). Yet, our understanding of the

inter-individual variability of the impact of light on brain function that would allow individual-tailored intervention is only partial. Maturation, development, aging may provide important clues. Collectively, the findings we reviewed underscore the complexity of light's impact on the brain across the lifespan and, most often, the insufficient amount of data to draw firm conclusions, particularly at younger ages. While teenagers and children are receiving increasing attention, studies in newborns and toddlers remain scarce and even inexistent for some aspects of the biological impact of light on brain function. Likewise, data in middle-aged individuals aged ~40y is rare and one can only infer based on younger or older individuals. Similarly, longitudinal studies monitoring several physiological aspects would allow better causal insights into the main factors underlying lifetime changes and, more generally, inter-individual differences in the NIF impact of light.

Figure 2-1 provides a summary of the changes we reviewed. An implication of the figure (and of the present review) is that, if the NIF impact of light changes over the lifespan, there is need for age-specific approaches when investigating the NIF effects of light. This is true also for field studies already bringing promises for the effectiveness of light interventions – in schools, hospitals, at work, patient institutions (Crowley et al., 2024; Giménez et al., 2017; Kawasaki et al., 2021; Riemersma-van der Lek, 2008; Stevenson et al., 2024). Similarly, response to light may be used as a marker for a disease trajectory (e.g. pupil size, PIPR and pupil constriction in Alzheimer's and Parkinson's diseases (El Haj et al., 2022; Joyce et al., n.d.). Likewise, light administration can also be considered a simple means to disturb/affect the brain. It can therefore provide insights about novel ecological means to improve the quality of brain function at different ages. All these promises warrant future fundamental investigation of lifetime changes and/or translation to the fields.

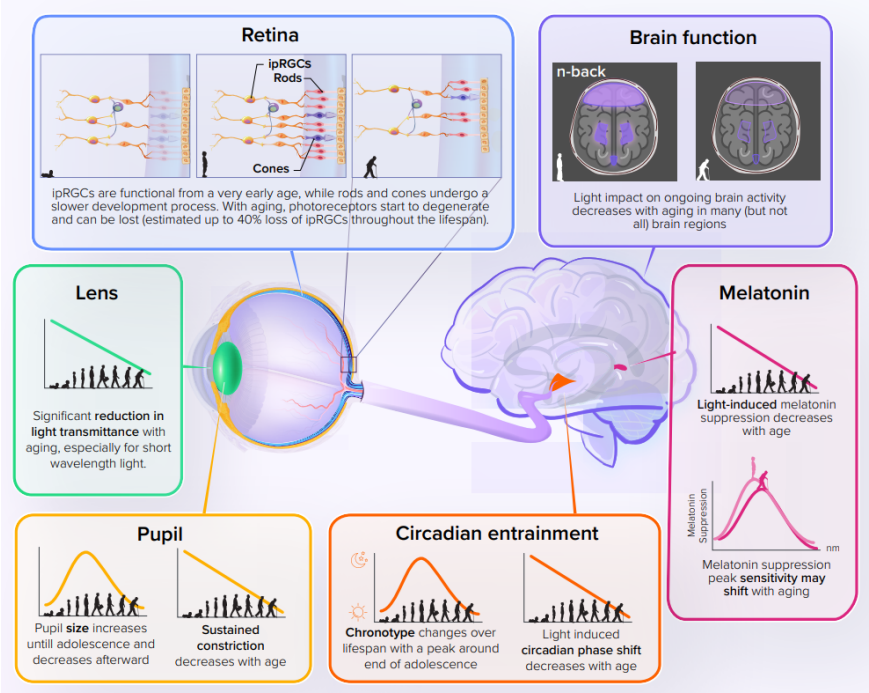
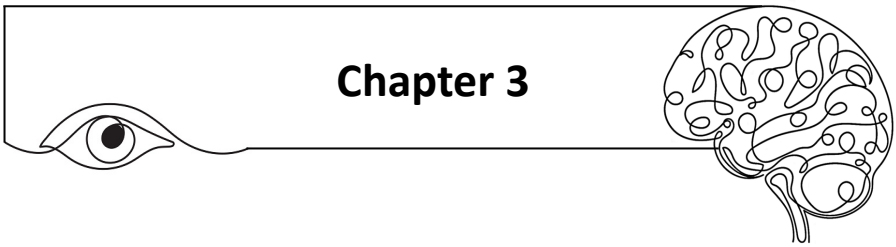


Figure 2-1: Lifetime changes in the biological impact of light on NIF brain functions.
Summary of the changes reviewed in the present paper. Refer to main text for full details.



Chapter 3

Research Framework

Thesis Objectives

As highlighted in the introduction, the increasing prevalence of LED lighting in our environment has dramatically altered the quality, intensity and timing of light in our environments, leading to significant changes in the amount and spectrum of light to which we are exposed. Unlike traditional light sources, modern LEDs are typically enriched in short-wavelength (blue) light, which has distinct biological effects beyond vision. Blue light, in particular, plays a crucial role in NIF effects (Vandewalle et al., 2007a, 2007b). The NIF effects of light on the brain are driven largely by photoreceptors in the retina that are sensitive to blue light and are called melanopsin-expressing ipRGCs (Brainard et al., 2001; Do, 2019; Thapan et al., 2001). These cells project to a variety of brain regions involved in regulation of circadian rhythms, sleep, alertness, mood, and cognitive function, such as the hypothalamus and thalamus (Do, 2019; Hattar et al., 2006; Scammell et al., 2017). While substantial research has documented the importance of these pathways, many unanswered questions remain. The precise neural circuits underlying these effects are not fully understood in humans and require further translation from animal models. Moreover, how NIF effects are modulated by multiple factors ranging from light characteristics to individual differences is not well understood. Among the many factors that can influence NIF effects, the focus of the current thesis is on developmental stage and time-of-day. These variables are critical because the sensitivity to light may differ between age groups, particularly during adolescence and early adulthood and the physiological response to light can vary based on time-of-day (Eto and Higuchi, 2023; Vandewalle et al., 2011a).

Existing research has predominantly focused on the general effects of light on circadian rhythms, sleep, alertness, melatonin suppression, mood and cognition, but the brain mechanisms underlying these effects, particularly across developmental stages and at different times of day, have not been fully explored.

As the use of light-based interventions grows across various industries, from healthcare to workplace design, gaining a detailed understanding of how light affects brain function and behavior is crucial. The growing interest in light interventions stems from their potential to optimize cognitive performance, improve sleep, and regulate mood, among other benefits. However, to fully realize the potential of light in real-world settings, it is essential to understand the specific mechanisms through which light influences NIF functions. This includes how different light characteristics, such as intensity, and timing, affect brain functions, and how individual factors, such as age, interact with these effects.

By targeting the objectives of the doctoral work, we wanted to contribute to the understanding of how modern light environments impact brain function. By examining brain regional activity, effective connectivity and cortical excitability, this thesis wants to provide a multi-dimensional view of the brain's response to light, specifically addressing the role of time-of-day and age-related changes in these effects. The results of this research may have important implications for public health and lighting design, particularly for adolescents, who may be at greater risk of adverse effects from evening light exposure. The findings could inform guidelines for safer lighting practices in schools, homes, and workplaces, optimizing lighting environments to support cognitive and emotional well-being while minimizing the negative consequences of modern light exposure.

Research Questions

The experimental part that follows consists of four chapters that are centered around 4 key research questions:

How Does Varying Illuminance Affect Hypothalamic Activity in the Morning?

In the first investigation, Chapter Four, we focused on the hypothalamus as it is the primary target of ipRGCs. This brain structure consists of several nuclei including SCN, VLPO, POA, LH, etc., each playing distinct roles such as circadian regulation, sleep promotion, wake regulation and other key functions. The hypothalamus is a small brain structure, which makes it challenging to image its distinct subregions using conventional fMRI. FMRI is a neuroimaging method that detects changes in blood oxygenation levels, which correlate with brain activity, offering insights into the brain function. In f/MRI, the higher the magnetic field strength, the finer the resolution of the images. Recent advancements in MRI technology, particularly the advent of ultra-high magnetic field MRI (UHF MRI), have made it possible to explore small structures like the hypothalamus in greater detail, with 7 Tesla (7T) MRI being the highest magnetic field strength currently approved for human brain imaging (FDA, 2017). However, despite this high resolution, the small size of hypothalamic nuclei still presents challenges in precisely targeting individual nuclei. As a preamble to the experimental section, we invite the reader to consult a technical discussion we published on the opportunities and limitations of 7T fMRI, as an editorial letter (**Appendix 1**).
With these technical advancements and limitations in mind, we aimed to investigate how varying levels of illuminance affect different regions (rather than individual nuclei) of the hypothalamus.

What Are the Differences in Hypothalamic Responses to Light Between Morning and Evening, and Between Adolescents and Young Adults?

The NIF effects of light are well known to be modulated by several factors, including the time-of-day with evidence from human studies suggesting some NIF aspects being typically stronger in the morning (Vandewalle et al., 2011a). Additionally, NIF responses to light vary across the lifespan, with research suggesting that adolescents may have a more pronounced response to light compared to adults (Eto and Higuchi, 2023). Building on the first investigation, Chapter Five examines whether the regional responses of the hypothalamus to light differ between morning and evening, as well as between adolescents and young adults.

How Does Light Exposure Modulate Brain Effective Connectivity, Specially Thalamo-Cortical Connectivity, and How Are These Modulations Influenced by Age and Time-of-Day?

In addition to brain activity itself, information flow between brain regions is crucial for brain function. We hypothesized that light may influence cognition and performance by modulating this information flow, or so-called functional connectivity, particularly between subcortical areas (e.g., thalamus) and cortical regions involved in cognitive tasks. In the final fMRI study, Chapter Six, we shifted the focus from examining the impact of light on regional brain activity to its effects on functional connectivity, which refers to the crosstalk between regions. However, rather than relying on conventional functional connectivity, which only measures correlations between regions, we employed effective connectivity, which provides insights into the causality of these interactions. To do this, we used Dynamic Causal Modeling (DCM) to assess how light influences the directed interactions between brain regions (Friston et al., 2003).

The thalamus plays a crucial role in information processing, and it has consistently been identified as an activated region in response to light in various studies (Gaggioni et al., 2014; Vandewalle et al., 2007a, 2007b). This suggests that the thalamus may be key in transmitting NIF signals to cortical regions, thereby contributing to the impact of light on cognition. Previous research of our team has shown that blue light modulates effective connectivity from the thalamus to cortical areas such as the intraparietal sulcus (IPS), influencing attention (Paparella et al., 2023). In this study, we used 7 Tesla fMRI to investigate the effects of different blue light intensities on a three-region network involving the mediodorsal nucleus (MDN) of the thalamus, the supramarginal gyrus (SMG) near

the IPS, and the inferior frontal junction (IFJ) next to the middle frontal gyrus (MFG), all regions implicated in executive functions. We also examined how varying blue light intensities, across different times of day and in adolescents versus young adults, influenced connectivity among these regions.

How Does Light Affect Cortical Excitability in Adolescents and Adults, as Measured by TMS-EEG?

Chapter Seven discusses a TMS-EEG study on cortical excitability, which reflects the cortical neurons' responsiveness to external stimuli. Cortical excitability is crucial for cognitive function because it reflects the brain's ability to process and integrate information. This measure is of particular interest as it may serve as an endpoint for understanding how light exposure affects cognition and brain function. Previous studies in this thesis have used fMRI to explore the effects of light on brain activity, specifically focusing on a subcortical region i.e. the hypothalamus (Chapters Four and Five) and on a thalamo-cortical network (Chapter Six). These studies established that light influences subcortical brain regions as well as subcortico-cortical connectivity. However, cortical excitability goes one step further, assessing how the brain responds to stimuli, making it a critical measure of the acute impact of light on cognitive function.

We used TMS-EEG to examine how different light conditions influence cortical excitability in both young adults and adolescents. TMS is a non-invasive technique that uses magnetic pulses to stimulate cortical neurons, effectively modulating their activity. When TMS is applied, the resulting changes in neural activity can be measured using EEG, which records electrical activity from the brain' surface. This combination allows us to capture real-time, high-resolution data on how light exposure alters neuronal excitability.

Cortical excitability was inferred from the amplitude and slope of the first EEG component (0–35 ms) of the TMS evoked potential (TEP) measured at the artifact-free stimulation spot. We predicted that higher light levels would enhance cortical excitability in young adults, and that this would correlate with improved cognitive performance. We further anticipated age-related differences in adolescents, though we did not predict the direction of these effects due to the unique developmental processes occurring in the adolescent brain.

By adding TMS-EEG to the investigation, this study expands on previous findings, looking beyond subcortical regional brain activity (measured by fMRI), and effective connectivity to examine the responses of the brain to light at the level of cortex. TMS-EEG provides a unique opportunity to

explore the neural mechanisms that may underlie cognitive performance changes associated with light exposure, offering insights into the functional dynamics of the brain that were not captured by traditional fMRI.

Overall protocol

The thesis will end with an overall section that in which we review the key findings of this thesis and attempt to place them within the context of existing research. We also reassess some of the study's limitations and, in conclusion, propose potential future directions for research on the non-image-forming effects of light.

Before exposing the different experimental chapters in the next section, we will explain briefly the overall protocol during which all the data were collected.

This research, as highlighted in the previous section on objectives, uses a multimodal approach, combining TMS-EEG and high-resolution 7 Tesla fMRI, to address part of the existing gap in our understanding of how light impacts brain function in humans. Specifically, it investigates the underlying mechanisms of NIF functions in adolescents compared to adults as well as at different times of day. The study involves three distinct participant groups:

- Adults undergoing fMRI in the morning (no TMS-EEG): 30 participants.
- Adults undergoing fMRI in the evening (with TMS-EEG): 17 participants.
- Adolescents undergoing fMRI in the evening (with TMS-EEG): 19 participants.

In total, sixty-six participants were involved in the study, though the number included in the analyses varied, as detailed in the individual chapters. Some adults participated in both morning and evening sessions, completing the TMS sessions as well. However, we soon realized that recruiting participants for both parts of the protocol was challenging, so we modified our approach to offer them the option to complete only part of the study. As a result, the final number of subjects included in the analyses differs across chapters.

All participants were first screened for the exclusion criteria and then completed a structural MRI session. The structural MRI served a dual purpose: it acted as a habituation process, allowing participants to adapt to the MRI environment before the functional scans and provided detailed anatomical data for neuronavigation during the TMS-EEG session.

fMRI protocol

To ensure consistent circadian entrainment across subjects while preventing excessive sleep deprivation and maintaining realistic conditions, participants followed a loose sleep-wake schedule for seven days prior to the fMRI session (±1 hour from their habitual bedtime/wake-up time). To standardize their short-term light history before the fMRI scan, participants underwent a 50-minute adaptation period on the experimental day upon arrival at the lab: 5 minutes of exposure to high-intensity white light (~1000 lux), followed by 45 minutes of dim light (<10 lux). During the fMRI session, participants completed three auditory cognitive tasks (executive, attentional, and emotional), while alternatively maintained in darkness (<0.01 lux) or short exposure (30-70 seconds) to monochromatic orange light (590 nm; 7.5 photopic illuminance lux; 0.16 melEDI lux) or polychromatic blue-enriched light (47, 116, 240 photopic illuminance lux; 37, 92, 190 melEDI lux). The inclusion of orange light in the protocol was intended to control for visual effects of light when analyzing the data, as ipRGCs are almost insensitive to this light. An eye-tracking system was used to ensure participants kept their eyes open and recorded pupil measurements throughout the tasks. However, due to the large volume of data and the involvement of multiple PhD students, pupil measurements were analyzed by other researchers (Beckers et al., 2024; Campbell et al., 2024a) and were not included in the studies presented in this thesis. For the same reason, the fMRI analyses in this thesis primarily focused on the executive task, except for the first study, which was a collaborative effort between two PhD students and included data from both the executive and emotional tasks.

As mentioned earlier, some participants underwent fMRI scans in the morning (adults), while others did so in the evening, allowing us to assess the impact of time-of-day. While adults were scanned either in the morning or evening, adolescents were only scanned in the evening for practical reasons. Conducting fMRI scans with adolescents in the morning would have probably required limiting scans to weekends, which could have introduced bias and extended the data collection process by restricting scans to only two days per week. The morning group was scanned approximately 2.5 hours after their habitual wake-up time, while the evening group was scanned about 1 hour before their habitual bedtime.

The fMRI scans were designed to cover the entire brain; however, in participants with larger head sizes, the upper part of the brain was not fully captured. However, the missing region was not relevant to our analysis (**Figure 3-1**).

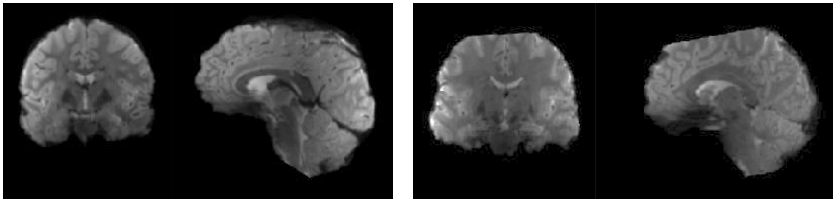


Figure 3- 1: fMRI coverage.
Subject with medium head size (left panel) and subject with large head size (right panel), shown as examples

TMS-EEG protocol

For the TMS-EEG session, participants followed a loose sleep schedule for five days prior to the experimental session. On the day of the experiment, participants arrived at the laboratory between 13:00 and 14:00. After the EEG cap was placed, they were kept in dim light (<10 lux) for almost 1.5 hours to control for recent light history. During this period, the TMS-EEG parameters were fine-tuned to ensure optimal signal quality and eliminate artifacts, allowing for reliable TMS-evoked potentials. Participants then completed three different light exposure sessions, each separated by an approximately 20-minute washout period in dim light (<10 lux). The TMS-EEG study included three light conditions: semi-monochromatic control orange light (580 nm; 30 photopic lux; 24 melEDI lux), low-intensity monochromatic blue light (470 nm; 30 photopic lux; 312 melEDI lux), and high-intensity monochromatic blue light (470 nm; 60 photopic lux; 625 melEDI lux). Each light session began with 1-2 minutes of light adjustment, followed by a 2-minute resting EEG recording, that in total led to approximately 5 minutes of pre-exposure (~1 minute for positioning the coil after the resting EEG) before the 10-minute TMS-EEG recording. The main goal of the TMS-EEG study was to assess the impact of blue light on cortical excitability in comparison to control orange light, both of which had the same photopic illuminance. The influence of blue light intensity (low vs. high) was an additional, secondary focus of the study. Due to the length of the entire protocol (approximately 5 hours), and the potential for fatigue, especially in adolescent participants, the high-intensity blue light session was always scheduled last to minimize the risk of early withdrawal before the final session. The order of the orange and low-intensity blue sessions was randomized to ensure unbiased results.

Since the TMS-EEG session was conducted in the afternoon, it did not disrupt participants' sleep schedules. For participants who completed both the fMRI and TMS-EEG sessions, those who started with the TMS-EEG protocol maintained their regular sleep schedule for two additional days

leading up to the fMRI session, ensuring a total of seven days of consistent sleep-wake cycles before the fMRI scan. In contrast, participants who began with the fMRI session followed a loose sleep schedule for seven days prior to the scan. Since the fMRI session took place at night and disrupted their sleep, these participants resumed their regular sleep schedule for five days before completing the TMS-EEG session. The overall protocol has been shown in **Figure 3-2**.

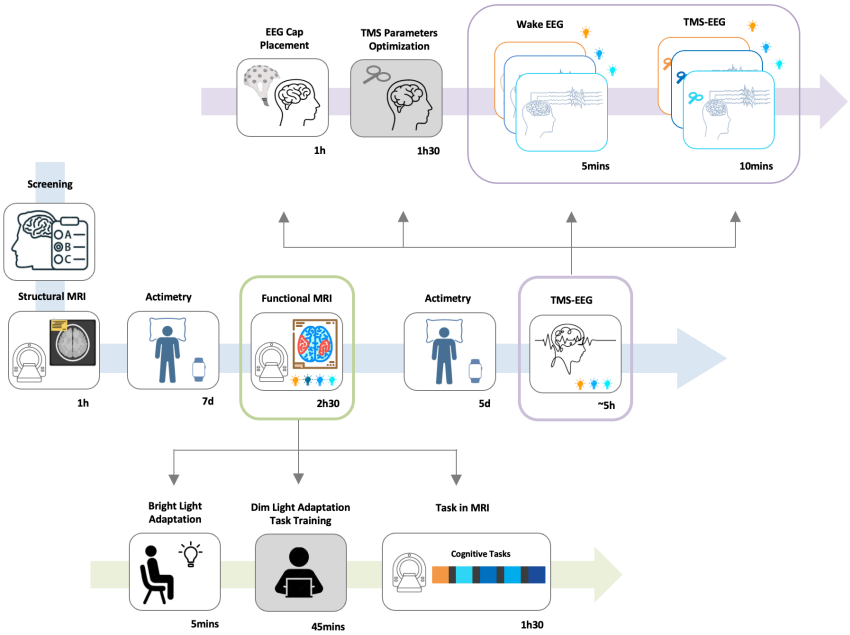
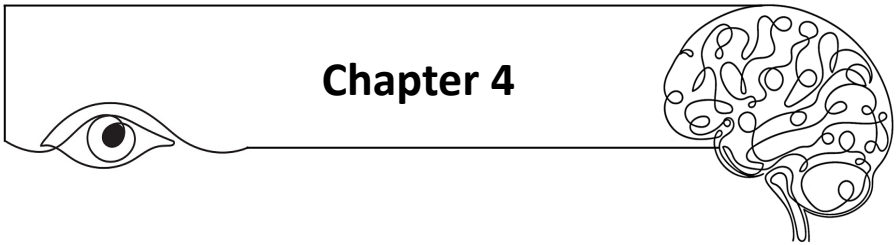


Figure 3- 2: ***Overall protocol of the study.***
This figure represents the protocol for those subjects who began with evening fMRI. For those who began with TMS-EEG, they followed their sleep-schedule for only 2 more days before doing the fMRI. Some participants did only fMRI in the morning



Chapter 4

Regional Response to Light Illuminance Across the Human Hypothalamus

This chapter is based on our published paper in eLife:

Campbell*, I., **Sharifpour*, R.**, Balda, F., 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. (2024) Regional response to light illuminance across the human hypothalamus, *eLife* 13:RP96576, https://doi.org/10.7554/eLife.96576.2

* Shared first-authorship

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 ± 2.9y) were completing two auditory cognitive tasks. We found 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 tuberomammillary 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.

Introduction

Light exerts multiple NIF biological effects that influence the quality of sleep and wakefulness, and higher illuminance is known to stimulate alertness and cognition (Campbell et al., 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 signaling 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 (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 (Do, 2019; Scammell et al., 2017). 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 (Do, 2019; Scammell et al., 2017).

The brain circuitry underlying the biological effects of light has mostly been uncovered in nocturnal rodent models (Campbell et al., 2023; Do, 2019). Translation to diurnal human beings, where the later maturation of the cortex allows for complex cognitive processing (Braak and 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 found 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.

Materials and 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., 2024; Campbell et al., 2024a; Paparella et al., 2023a). 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; **Suppl. Table 9-1**) 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; color 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) (Aaron T. Beck et al., 1988), and <14 on the Beck Depression Inventory-II (up to mild depression) (Beck et al., 1988a), < 12 on the Epworth Sleepiness Scale (Johns, 1993), and < 8 on the Pittsburgh Sleep Quality Index (PSQI) (indicating good sleep quality) (Buysse et al., 1989). We further assessed chronotype with the Horne-Östberg questionnaire (Horne and Ostberg, 1976) and seasonality with the Seasonal Pattern Assessment Questionnaire (Rosenthal, 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. **Suppl. Table 9-1** summarizes 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 standardize 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 4-1 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.

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 fiber which was attached to a stand fitted at the back of the MRI coil that allowed reproducible fixation and orientation of the optic fiber 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, M, USA) and optical fiber filters (monochromatic narrowband orange filter – 589 nm; 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 4-1 B and Suppl. Table 9-2** for in-detail light characteristics).

Illuminance and spectra could not be directly measured within the MRI scanner due to the ferromagnetic nature of measurement systems. The coil of the MRI and the light stand, together with the lighting system were therefore placed outside of the MR room to reproduce the experimental conditions of the in a completely dark room. A sensor was placed 2 cm away from the mirror of the coil that is mounted at eye level, i.e. where the eye of the first author of the paper would be positioned, to measure illuminance and spectra. The procedure was repeated 4 times for illuminance and twice for spectra and measurements were averaged. This procedure does not take into account inter-individual variation in head size and orbit shape such that the reported illuminance levels may have varied slightly across subjects. The relative differences between illuminance are, however, very unlikely to vary substantially across participants such that statistics consisting of tests for the impact of relative differences in illuminance were not affected. The detailed values reported in Supplementary Table 2 were computed combining spectra and illuminance using the excel calculator associated with a published work (Lucas et al., 2014).

Blue-enriched light illuminances were set according to the technical characteristics of the light source and to keep the overall photon flux similar to prior 3T MRI studies of our team (between ~1012 and 1014 ph/cm2/s) (Vandewalle et al., 2011b, 2010). The orange light was introduced as

a control visual stimulation for potential secondary whole-brain analyses. For the present region of interest analyses, we discarded color differences between the light conditions and only considered illuminance as indexed by melEDI lux. This constitutes a limitation of our study as it does not allow attributing the findings to a particular photoreceptor class.

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 melEDI lux; 6500K) and one illuminance level of monochromatic orange light (0.16 melEDI lux; 590 nm full width at half maximum -FWHM: 10 nm). For the present analyses, we discarded color differences between the light conditions and only considered illuminance as indexed by melEDI 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 melEDI lux) and one illuminance level of the monochromatic orange light (0.16 melEDI 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.

Cognitive Tasks

Prior work of our team showed that the n-back task and emotional task included in the present protocol were successful probes to demonstrate that light illuminance modulates cognitive activity, including within subcortical structures (though resolution did not allow precise isolation of nuclei or subparts) (e.g. (Vandewalle et al., 2010, 2007b)). When taking the step of ultra-high-field imaging, we therefore opted for these tasks as our goal was to show that illuminance affects brain activity across cognitive domains while not testing for task- specific aspects of these domains. Auditory cognitive 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) 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-randomized across the 4 light conditions with 3 blocks of 0-back and 4 blocks of 2-back per light condition (see **Figure 4-1 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 prosody. 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 behavioral assessments (Banse and 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 4-1 D**).

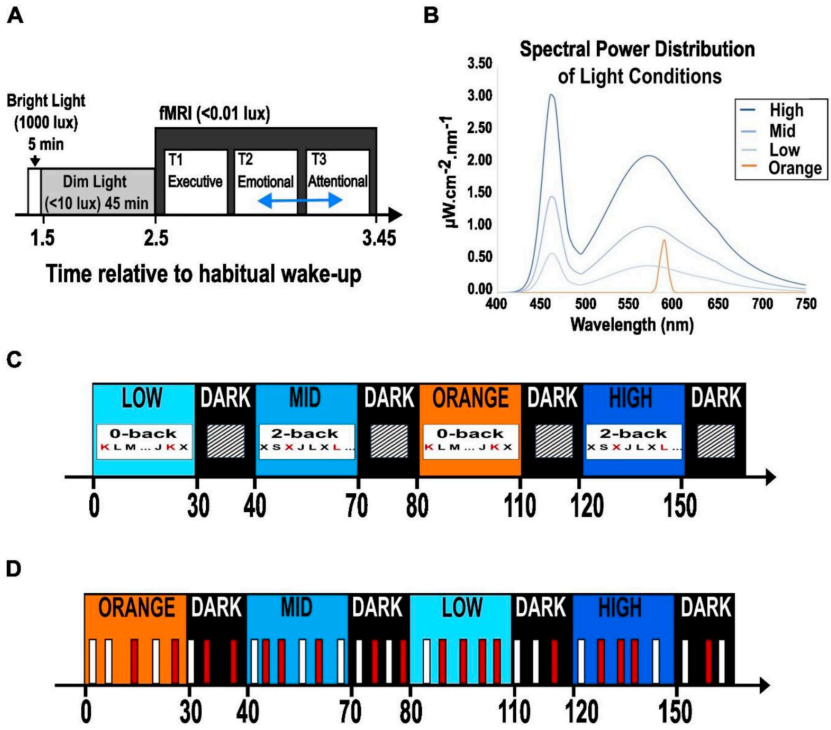


Figure 4-1: Experimental protocol.
(A) Overall timeline. After prior light history standardization, participants performed executive (always first), emotional and attentional tasks (pseudo-randomly 2nd or 3rd, blue arrow). As the attentional task included fewer light conditions, it is not considered in the present manuscript (see methods for more details). (B) Spectral power distribution of light exposures. Monochromatic orange: 0.16 melEDI lux; Polychromatic, blue-enriched light (6500K); LOW, MID, HIGH: 37, 92, 190 melEDI lux. For the present analyses, we discarded color differences between the light conditions and only considered illuminance as indexed by melEDI lux, constituting a limitation of our study (See Suppl. Table 9-2 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)).

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 inhomogeneity 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 (O'Brien et al., 2014) of Statistical Parametric Mapping 12 (SPM12) under Matlab R2019 (MathWorks, Natick, Massachusetts). 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 and Friston, 2005). To ensure optimal co-registration, brain extraction was done using SynthStrip (Hoopes et al., 2022) implemented 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 4-2 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 = 3 mm. 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 256s 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 (0.16, 37, 92, 190 melEDI). 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 melEDI). The contrasts of interest consisted of the main effects of each regressor. The output masks of the segmentation procedure were used to extract regression betas associated with each of the hypothalamus subparts using the REX Toolbox (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 visualization 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 Generalized 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 melEDI 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) (Faul 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; **Suppl. Table 9-1**) 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 - melEDI- lux; **Suppl. Table 9-2**) (**Figure 4-1**). The hypothalamus of each participant was segmented into 5 subparts – inferior-anterior, superior-anterior, inferior-tubular, superior-tubular, and posterior (**Figure 4-2 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 4-2 B, C**; **Table 4-1)**. A nominal main effect of the task was detected for the emotional task ($p = 0.048$; **Table 4-1)** but not for the n-back task. For both tasks, there was no significant main effect for any of the other 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 ($p_{corrected} \leq 0.05$, **Table 4-1)**. 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 4-2 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.

Table 4-1: 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**	**P value**	**Partial R^2**	**Contrast**	**t-value**	**$P_{uncorrected}$**	**$P_{corrected}$ (Tukey)**
Hypothalamus subparts	4.36	**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	0.4		1 vs. 5	-0.57	0.57	0.98
Hypothalamus subparts x task type	0.68	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	0.57		3 vs. 4	3.48	**0.0006**	**0.0055**
BMI	0.59	0.45		3 vs. 5	2.54	**0.0041**	**0.033**
Sex	0.01	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**	**$P_{uncorrected}$**	**$P_{corrected}$ (Tukey)**
Hypothalamus subparts	9.38	**<.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	0.048		1 vs. 5	-2.24	**0.025**	0.17
Hypothalamus subparts x stimulus type	0.55	0.74		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	0.67		3 vs. 4	4.71	**< 0.0001**	**< 0.0001**
BMI	0.05	0.82		3 vs. 5	2.52	**0.013**	0.091
Sex	1.54	0.23		4 vs. 5	-2.19	**0.03**	0.19

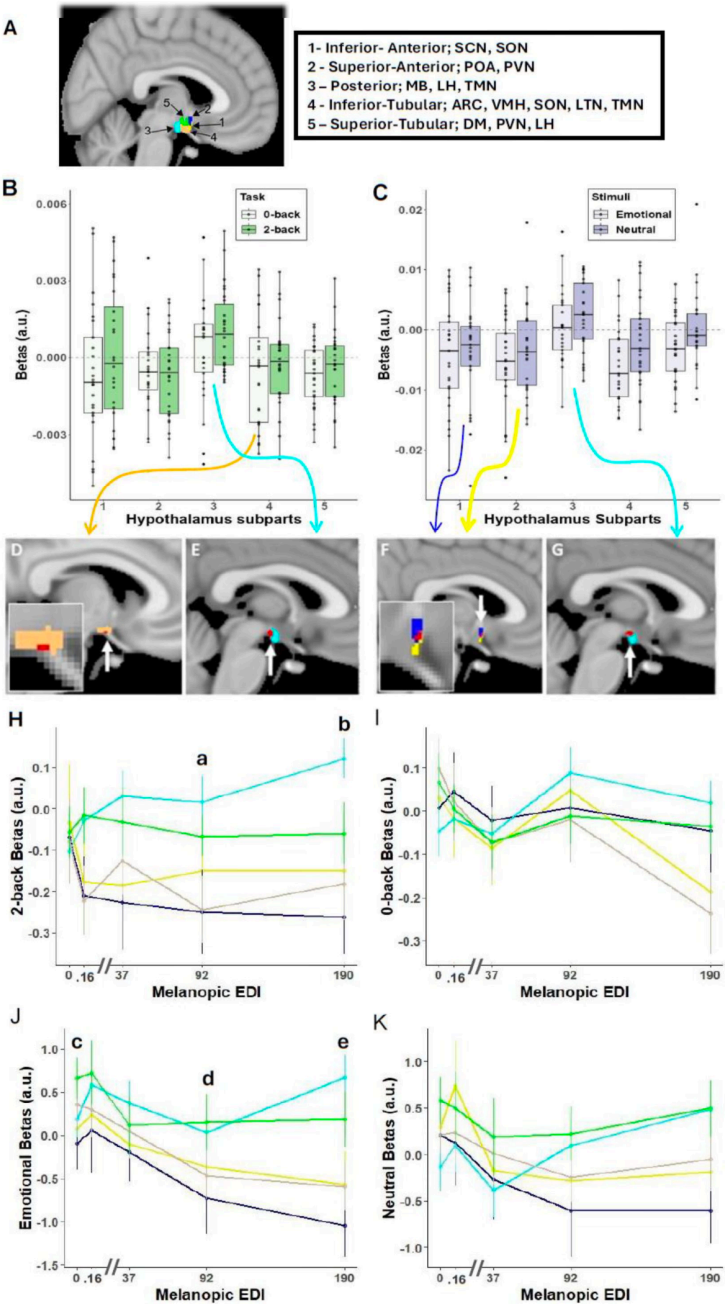

A
1- Inferior- Anterior; SCN, SON
2 - Superior-Anterior; POA, PVN
3 – Posterior; MB, LH, TMN
4 - Inferior-Tubular; ARC, VMH, SON, LTN, TMN
5 – Superior-Tubular; DM, PVN, LH
B
Task
0-back
2-back
Betas (a.u.)
Hypothalamus subparts
C
Stimuli
Emotional
Neutral
Betas (a.u.)
Hypothalamus Subparts
D
E
F
G
H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

Figure 4-2: 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 1 for full statistics). (B) Executive task: significant main effect of hypothalamus subparts (p=0.002), no significant main 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), and of stimulus type (p=0.048) or subpart-by-stimulus-type interaction (p=0.74).
(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 color 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.
(H-K) Estimates of the impact of each illuminance on the activity of the hypothalamus subparts. (Refer for Table 4-2 and Suppl. Tables 9-3 to 9-6 for full statistics). Activity dynamics across illuminance for each subpart (color 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 (H-I) the executive task (p=0.041) and (J-K) the emotional task (p=0.041). Small letter indicate significant difference (p < 0.05) between the following subparts at illuminance: a. 92 melEDI lux: posterior vs. superior-anterior & inferior-tubular; b. 190 melEDI lux: posterior vs. inferior-anterior, superior-anterior & inferior-tubular; c. 0 melEDI lux: posterior vs. superior-tubular; d. 92 melEDI lux: posterior vs. superior- anterior; superior-anterior vs. superior-tubular; e. 190 melEDI lux: posterior vs. inferior-anterior, superior-anterior & inferior- tubular; superior-tubular vs. superior-anterior, inferior-tubular & inferior-anterior.

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 4-2 H-K**; **Table 4-2**). Post hoc contrasts first considered the impact of the changes in illuminance within each subpart (**Suppl. Tables 9-3, 9-4**). The activity of the posterior hypothalamus subpart significantly (p <0.05) increased under the highest illuminance (190 melEDI) compared with darkness for both tasks and with the lower illuminances (37 and 92 melEDI 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 the lower illuminance (0.16 melEDI lux) 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 4-2** ; **Suppl. Tables 9-5, 9-6**). For both tasks, the activity of the posterior hypothalamus subpart was consistently significantly higher than the activity of the inferior-tubular subpart under the highest illuminances (92 and 190 melEDI 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 melEDI 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 melEDI 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/or 190 melEDI lux). The overall picture arising from these comparisons is that higher illuminance increased the activity of the posterior hypothalamus subpart while it decreased the activity of the inferior-tubular and anterior hypothalamus subparts.

Table 4-2: 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**	**P value**	**Partial R^2**	**Illuminance***	**contrast**	**t-value**	**p-value**
Subpart	1.4	0.23		92	2 vs. 3	-2.25	**0.025**
Illuminance	2.15	0.073		92	3 vs. 4	2.58	**0.01**
				190	1 vs. 3	-2.80	**0.0053**
Task	3.24	0.073		190	2 vs. 3	-2.24	**0.025**
Subpart x Illuminance	1.7	**0.041**	**0.09**	190	3 vs. 4	3.15	**0.0017**
Age	1.19	0.29					
BMI	0.01	0.9					
Sex	0.38	0.54					

Emotional task							
Main GLMM				Comparisons between subparts per illuminance #			
Effect	**F-value**	**P value**	**Partial R^2**	**Illuminance***	**contrast**	**t-value**	**p-value**
Subpart	4.29	**0.0023**	**0.07**	0	3 vs. 5	-2.05	**0.04**
				92	2 vs. 3	-2.53	**0.012**
Illuminance	9.41	**< 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	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	**0.041**	**0.026**	190	4 vs. 5	-2.32	**0.021**
Age	0.59	0.45					
BMI	1.54	0.23					
Sex	0.05	0.83					

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 R^2 215 = 0.1; **Figure 4-3 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 R^2 219 = 0.09). Surprisingly, the association was negative (**Figure 4-3 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 subpart activity; F < 0.62; p > 0.4; **Figure 4-3 C,D**; **Suppl. Table 9-7**). 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 4-3 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 4-3 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 4-3 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 reaction times (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 4-3 H**).

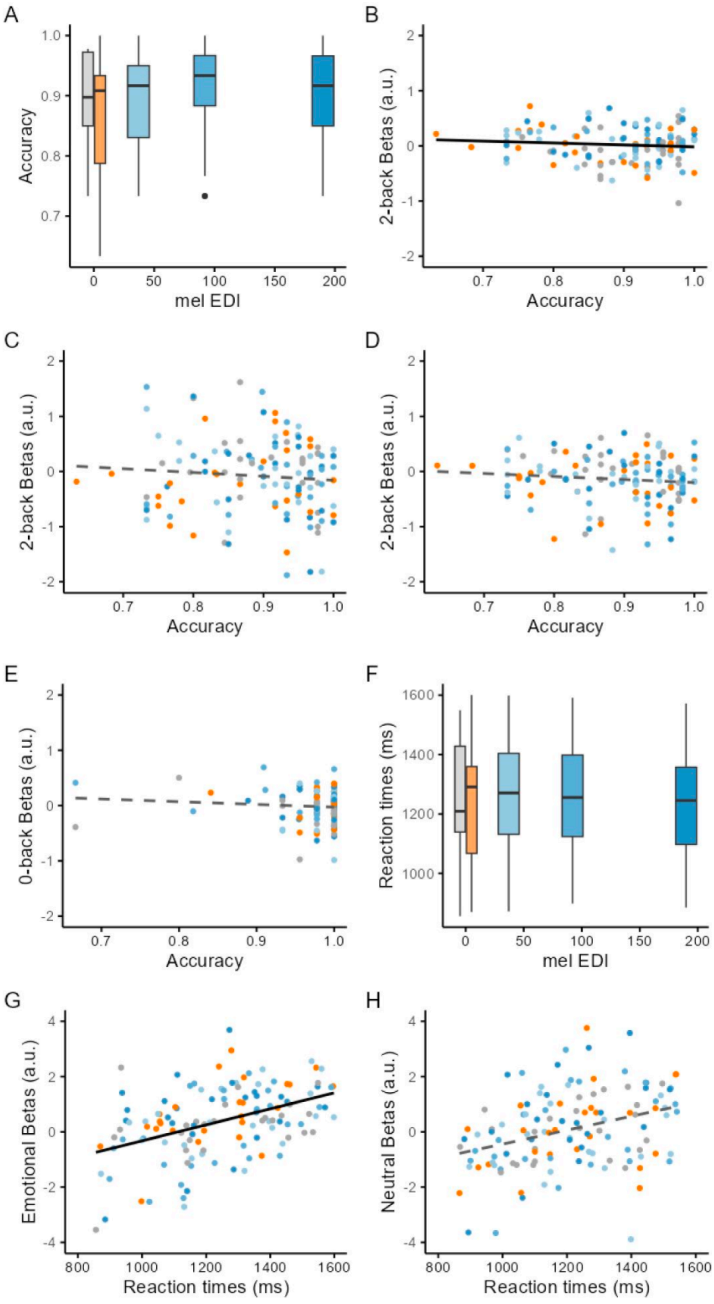

A
Accuracy
mel EDI
B
2-back Betas (a.u.)
Accuracy
C
2-back Betas (a.u.)
Accuracy
D
2-back Betas (a.u.)
Accuracy
E
0-back Betas (a.u.)
Accuracy
F
Reaction times (ms)
mel EDI
G
Emotional Betas (a.u.)
Reaction times (ms)
H
Neutral Betas (a.u.)
Reaction times (ms)

Figure 4-3: 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 Suppl Table 9-7 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.

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 et al., 2023; Do, 2019; Hattar et al., 2006; Scammell et al., 2017). 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 (Do, 2019; Hattar et al., 2006). 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. The pattern of light-induced changes was consistent across an executive and an emotional task which consisted of a block and an event-related fMRI design, respectively. This suggests that a robust anterior-posterior gradient of activity modulation by illuminance is present in hypothalamus across cognitive domains. 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., 2022a). 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 (Do, 2019; Hattar et al., 2006; Scammell et al., 2017). 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. In line with this assumption, chemoactivation of ipRGCs lead to increase c-fos production, a marker of cellular activation, over several nuclei of the hypothalamus, including the lateral hypothalamus (Milosavljevic et al., 2016). If this initial effect of light we observe over the posterior part of the hypothalamus was maintained over a longer period of exposure, this would stimulate cognition and maintain or increase alertness (Campbell et al., 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 melEDI 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. Chemoactivation of ipRGCs in rodents led to an increase activity of the SCN, over the inferior anterior hypothalamus, but had no impact on the activity of the VLPO, over the superior anterior hypothalamus (Milosavljevic et al., 2016). How our findings fit with these

fine-grained observations and whether there are species-specific differences in the responses to light over the different part of the hypothalamus remains to be established. The inferior-tubular and inferior-anterior subparts of the hypothalamus – that we isolated also 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 be the results of an inhibitory signal from a subclass of ipRGCs, potentially through the release aminobutyric acid (GABA), as a rodent study found that a subset of ipRGCs release GABA at brain targets including the SCN (and intergeniculate leaflet and ventral lateral geniculate nucleus), leading to a reduction in the ability of light to affect pupil size and circadian photoentrainment (Sonoda et al., 2020). Whatever the signaling of ipRGC, our finding over the anterior hypothalamus could correspond to a modification of GABA signaling of the SCN which has been reported to have excitatory properties, such that the BOLD signal changes we report may correspond to a reduction in excitation arising in part from the SCN (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 superior-anterior hypothalamus subpart of the hypothalamus encompassing the VLPO and PON sees its activity decreasing under higher illuminance during the emotional task, similarly to the inferior-anterior 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.

Subcortical structures, and particularly those receiving direct retinal projections, including those of the hypothalamus, are likely to receive light illuminance signal first before passing on the light modulation to the cortical regions involved in the ongoing cognitive process (Campbell et al., 2023). A critical aspect of our results is that the performance to the 2-back (executive) subtask was

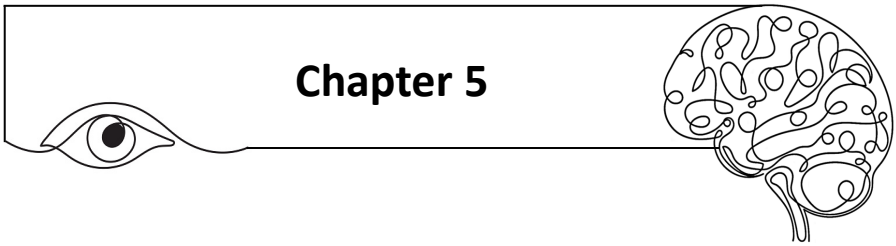
significantly increased when exposed to higher illuminance light. The extent of this increase was limited, likely because performance was overall high at all illuminances, but was not detected for the simpler detection letter subtask (0-back). The result contrasts with many previous 3T MRI investigations on the biological effects of light on human brain function which did not report behavioral changes induced by repeated short exposures to light (e.g. (Vandewalle et al., 2011b, 2007b, 2007a) 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 behavioral 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 behavioral response to emotional stimuli. The association between behavior 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 behavior, which intrinsically primarily depends on cortical activity.

Future research may consider data-driven analyses of u234748 voxels time series as an alternative to the parcellation approach we adopted here. This may refine the delineation of the subparts of the hypothalamus undergoing decreased or increased activity with increasing illuminance. Future research should also 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 behavioral 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 (Paparella et al., 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 (Do, 2019; Güler et al., 2008). Given the polychromatic nature of the light we used, classical photoreceptors and their projections to visual brain areas are, however, very likely to have directly or indirectly contributed to the modulation by light of the regional activity of the hypothalamus. Furthermore, we cannot exclude that color and/or spectral differences between the orange and 3 blue-enriched light conditions may have contributed to our findings. Research in rodent models demonstrated that variation in the spectral composition of light was perceived by the suprachiasmatic nucleus to set circadian timing (Walmsley et al., 2015). No such demonstration has, however, been reported yet for the acute impact of light on alertness, attention, cognition or affective state. Future human studies could isolate the contribution of each photoreceptor class to the impact of light on cognitive brain functions by manipulating prior light history (Chellappa et al., 2014) or through the use of silent substitutions between metameric light exposures (Viénot et al., 2012).

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; Münch et al., 2017; Riemersma-van der Lek, 2008; Scheuermaier et al., 2018; Wirz-Justice and Benedetti, 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 5

Consistent Regional Hypothalamic Response to Illuminance with Time of Day but not with Developmental Age

This chapter is based on our paper under preparation:

Sharifpour, R., Campbell, I., Balda, F., Beckers, E., Paparella I., Read, J., Mortazavi, N., Koshmanova, E., Zubkov, M., Talwar, P., Collette, F., Phillips, C., Lamalle, L., Vandewalle, G. (2024)

Abstract

Light plays a significant role in regulating various non-visual biological processes, such as enhancing alertness and wakefulness. However, the precise subcortical neural pathways, especially concerning how these processes are modulated by time-of-day and developmental stages, remain poorly understood. In this study, we used 7 Tesla functional magnetic resonance imaging to examine the impact of varying light illuminance on the hypothalamic activity. Healthy young adults (N=33; 22 women; 24.8 ± 3.2y) and adolescents (N=16; 6 women; 16.8 ± 1.1y) were scanned in the morning and in the evening while they completed an auditory executive task under different light conditions (0.16, 37, 92, 190 melanopic equivalent daylight illuminance- melEDI lux). In young adults and during both evening and morning light exposure, varying illuminance induced distinct regional activity changes within the hypothalamus, with the posterior hypothalamus showing increased activity, while the anterior hypothalamus exhibited a decrease. Adolescents exhibited similar patterns, showing an opposite response in the posterior compared to the anterior hypothalamus, however, the magnitude of hypothalamic response at the highest illuminance, particularly the deactivation of the superior-anterior and inferior-tubular hypothalamus, were greater in this group than in young adults. These findings reveal the complex, non-uniform regulation of hypothalamic activity by light, demonstrating age-related differences in light responsiveness and providing novel insights into how light influences hypothalamic neural circuits across different developmental stages.

Introduction

Light exerts multiple impacts on human physiology, extending beyond vision, through non-image-forming (NIF) effects that regulate key biological processes, including circadian rhythms, sleep-wake regulation, alertness, mood and cognitive function (Campbell et al., 2023). These NIF effects are largely mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs), a specialized class of retinal ganglion cells (RGCs) that are maximally sensitive to short-wavelength (blue) light with wavelength of ~480 nm (Do, 2019). IpRGCs compile their intrinsic photosensitivity to signal of rods and cones to relay light signals to a wide range of brain regions. A critical target of ipRGCs signals is the hypothalamus, a brain region coordinating NIF effects on physiological states such as arousal, sleep-wake regulation, and cognitive functioning (Daneault et al., 2016; Scammell et al., 2017). Several distinct hypothalamic nuclei are innervated by ipRGCs, including the anterior part with the suprachiasmatic nucleus (SCN), the master circadian pacemaker, and ventrolateral

preoptic nucleus (VLPO), which promotes sleep, as well as the lateral and posterior part with the lateral hypothalamus (LH) containing both wake and sleep promoting neurons (Hattar et al., 2006; Milosavljevic et al., 2016; Zhang et al., 2021). These nuclei are considered to play key roles in modulating light's effects on arousal, alertness, and cognitive performance. Much of our understanding of light's impact on the hypothalamus nuclei comes, however, from animal studies (Campbell et al., 2023; Do, 2019), where the neural circuits can be invasively studied and manipulated. Translating these findings to humans is not straightforward, due to differences in anatomy, physiology, and the complexity of human cortex (Galakhova et al., 2022). Confirming a first task-free fMRI study (Schoonderwoerd et al., 2022), we recently reported that the anterior part of the hypothalamus largely encompassing the SCN sees its activity decrease with increasing illuminance during cognitive tasks (Campbell et al., 2024b). In contrast the posterior part, including part of the LH, showed the opposite pattern with increasing activity at higher illuminance. Besides these first studies, the exact regional dynamics of hypothalamic activity in response to varying light conditions in humans remains to be established.

Light impact on circadian entrainment is well known to depend on time-of-day (Campbell et al., 2023) while the stimulating effect of light on alertness and cognition may also vary with time-of-day , including in humans (Vandewalle et al., 2011a; Vimal et al., 2009). This is related to differential SCN responses to light in animals studies, but the hypothalamic correspondence is not known in humans. Moreover, brain development has been reported to influence NIF effects (Campbell et al., 2023). Adolescents may exhibit different sensitivity and neural responses to light compared to adults (Eto and Higuchi, 2023). This contributes to the current concerns about adolescent screen device consumption, particularly in the evening. Whether these concerns are founded is unclear. Investigating hypothalamus responses to illuminance changes may help resolve the issue.

In this study, we took advantage of high-resolution 7-Tesla functional magnetic resonance imaging (fMRI) to investigate how the regional impact of light illuminance within the hypothalamus changed with time-of-day and between adolescence and early adulthood. Specifically, we sought to determine whether the hypothalamic response of young adults (19-30y) to light varied from the morning to the evening. Because of the current concerns with evening light exposure in adolescents, we further included a group of late teenagers (15-18y) that completed the protocol in the evening. While our initial study included both an executive and an emotional task, we only focused on the executive task in the current investigation as it was previously successfully used to uncover time-of-day change in the impact of light on NIF brain function (Vandewalle et al., 2011a)

and also to avoid multiplying the factors of interest in a single paper. The emotional task will be subjected to a warranted subsequent analyses.

Material and Method

This cross-sectional research is part of a broader investigation that has led to multiple publications using part of or all the adult participants included in the present paper (Beckers et al., 2024; Campbell et al., 2024b, 2024a; Paparella et al., 2023). All procedures and analyses are as in (Campbell et al., 2024b), except for participant groups and analyses pertaining to group comparisons. The Ethics Committee of the University of Liège approved the study. All participants gave written informed consent and were financially compensated for their participation.

Participants

This study involved 55 healthy participants aged 15 to 30 years (22.0 ± 4.6 years; 29 females) recruited between December 2020, and September 2023. The study consists of between group comparisons including 3 non-overlapping groups of participants: 20 young adult completed the protocol in the morning (24.1 ± 2.5 years; 13 females; 19 participants were included in our initial publication), with the fMRI session taking place approximately 2.5 hours after their habitual wake-up time; 17 young adults completed the protocol in the evening (25.2 ± 4.0 years; 10 females; 6 participants were included in our initial publication but with their data collected in the morning), with fMRI sessions approximately 1 hour before their habitual bedtime; 18 adolescent completed the protocol in the evening (16.7 ± 1.1 years; 6 females), underwent fMRI scanning approximately 1 hour before their habitual bedtime. Exclusion criteria for all groups included a BMI>28, recent psychiatric history, sever trauma, sleep disorders, addiction, chronic medication use, excessive alcohol alcohol consumption (>14 units/week), and high caffeine intake (>4 cups/day). Participants were also excluded if they had chronic night shift work in the past year, transmeridian travel in the past two months, or any history of ophthalmic disorders. Participants were included if they scored below 18 on the 21-item Beck Anxiety Inventory (BAI) (indicating mild anxiety or less) (Morin et al., 1999), below 14 on the Beck Depression Inventory-II (BDI-II) (indicating mild depression or less) (Beck et al., 1988), below 8 on the Pittsburgh Sleep Quality Index (PSQI) (indicating good sleep quality) (Buysse et al., 1989), and below 12 on the Epworth Sleepiness Scale (ESS) (indicating normal daytime sleepiness) (Johns, 1993). Participants also completed questionnaires assessing chronotype (Horne-Östberg) (Horne and Ostberg, 1976), and seasonal mood variation (Seasonal

Pattern Assessment Questionnaire - SPAQ) (Rosenthal, 1984), but these were not used for participant inclusion. Demographic details of the participants included in the analyses are summarized in **Table 5-1**.

Table 5-1: Demographic characteristics of the participants included in the analyses.

	Adults_Morning (AM)	Adults_Evening (AE)	Asolescents (T)	Comparison (t-test)	
				AM vs AE	AE vs T
Number of Subjects	18	15	16		
Age (mean±SD)	23.9±2.3	25.2±4.0	16.8±1.1	P=0.23	**P<0.0001**
Sex: Female (Male)	12(6)	10(5)	6(10)	P=0.64	P=0.18
Body mass index (kg/m^2)	21.4±2.3	22.1±2.0	21.8±2.1	P=0.35	P=0.69
Depression (BD-II[a])	5.6±5.6	6.6±3.5	6.2±4.8	P=0.57	P=0.81
Anxiety Level (BAI[b])	5.3±6.5	5.5±3.3	6.6±7.0	P=0.89	P=0.59
Chronotype (HO[c])	51.8±7.2	43.1±7.3	43.4±7.7	**P=0.002**	P=0.93
Sleep Quality (PSQI[d])	3.6±2.9	4.1±1.9	4.1±1.6	P=0.62	P=0.96
Habitual daytime Sleepiness (ESS[e])	5.7±3.0	6.9±2.4	6.0±4.5	P=0.23	P=0.52
Season of experiment *	-0.1±0.7	-0.4±0.5	-0.4±0.6	P=0.08	P=0.70
Seasonality (SPAQ[g])	1.0±0.8	1.3±0.9	0.7±1.0	P=0.37	P=0.24

[a]. Beck's Depression Inventory II
[b]. Beck's Anxiety Inventory
[c]. Horne and Östberg Questionnaire
[d]. Pittsburg Sleep Quality Index
[e]. EPWORTH Sleepiness Scale
[f]. Seasonal Pattern Assessment Questionnaire
* Cosine (acquisition day of year*360/365) : 21 December=0°
** All participants in all groups were right-handed.

Study Design and Procedure

To prevent excessive sleep deprivation while maintaining realistic conditions, participants were instructed to follow a loose sleep-wake schedule for seven days prior to their laboratory visit, with bed and wake-up times restricted to within ±1 hour of their habitual schedule. Compliance was verified using actigraphy (AX3 accelerometer, Axivity, United Kingdom) and daily sleep diaries.

Additionally, participants were requested to refrain from all caffeine and alcohol-containing beverages, as well as extreme physical activity for 3 days before participating in the fMRI acquisition. The timing of the experiments varied based on group assignment: morning session started about 2.5 hours after the participants' habitual wake-up time, and evening session started roughly 1 hours before their habitual bedtime. Upon arrival, all participants underwent a light adaptation protocol to standardize recent light exposure before the fMRI scan. This involved 5 minutes of exposure to high-intensity white light (~1000 lux), followed by 45 minutes of dim light (<10 lux). During this period, participants received instructions and completed practice trials of the cognitive task (n-back) on a laptop under dim light conditions (**Figure 5-1 A**).

Inside the scanner, an auditory letter variant of the n-back task, a well-established measure of working memory (Collette et al., 2005), was presented to participants. In the letter detection 0-back condition, participants were instructed to respond whenever the current auditory stimulus (a letter) matched a predefined target letter (the letter “K”). This condition served as a baseline to control for baseline brain activity. In the 2-back condition, participants were required to continuously update and maintain relevant information in working memory. They had to identify whether the current letter matched the letter presented two items earlier. The task was delivered in a block design, alternating in a pseudo-random manner (ensuring spread of each block task over the entire recording) between blocks of 0-back and 2-back tasks (38 blocks in total consisting of 19 blocks of 0-back and 19 blocks of 2-back), yielding a total task duration of approximately 25 minutes. Participants responded using an MRI-compatible keypad held in their dominant hand. Auditory stimuli were delivered through noise-cancelling, MRI-compatible headphones to ensure clear auditory perception despite the MRI noise. The n-back was followed by an emotional and an attentional task which will not be discussed in the present paper.

Participants were alternately maintained in darkness (<0.01 lux) or exposed to blue- enriched cool polychromatic light (6500K) at varying illuminance levels (37, 92, 190 melEDI lux), and a control monochromatic orange light (590 nm; 0.16 melEDI lux), to which ipRGCs are nearly insensitive (**Figure 5-1 B**). The orange light was introduced as a control visual stimulation for potential secondary whole-brain analyses. For the present region of interest (ROI) analyses, we discarded color differences between the light conditions and only considered illuminance as indexed by melEDI lux. This constitutes a limitation of our study as it does not allow attributing the findings to a particular photoreceptor class.

The detailed methodology for light set-up and its delivery into the MRI scanner can be found in our previous publication (Campbell et al., 2024b; Paparella et al., 2023). There were 8 blocks per

light condition and 6 blocks for the darkness condition. There were also darkness periods (~10 seconds, <0.01 lux) without task between blocks with different light conditions to ensure that the light exposure in one block did not affect brain activity in the subsequent block. During all fMRI sessions, pupil size was measured simultaneously with an eye-tracking device (SR-Research, anada). Eye tracking confirmed that participants kept their eyes open during the scan. The entire experiment was designed using OpenSesame (Mathôt et al., 2012).

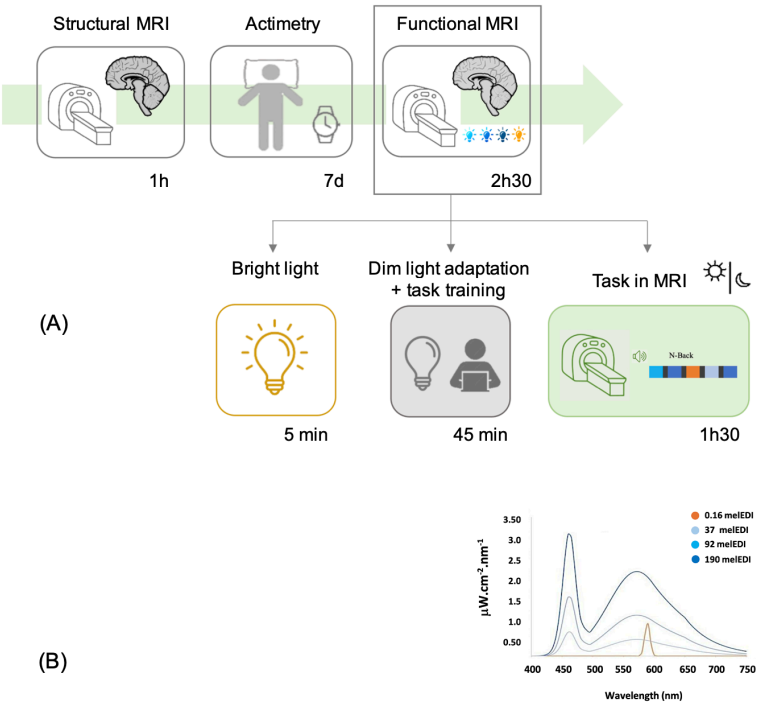


Figure 5-1: Graphical representation of the experimental protocol along with the spectrum of light conditions.
Orange light (0.16 melEDI lux), and three intensities of blue-enriched light (37, 92, 190 melEDI lux).

MRI Data Acquisition

Structural and functional MRI data were obtained using a MAGNETOM Terra 7T MRI system (Siemens Healthineers, Erlangen, Germany) equipped with a 32-channel receive and a 1-channel

transmit head coil. To minimize dielectric artifacts, dielectric pads (Multiwave Imaging, Marseille, France) were positioned between the participants' heads and the receiver coil. A multi-band Gradient-Recalled Echo - Echo-Planar Imaging (GRE-EPI) sequence was utilized to collect multislice T2*-weighted fMRI images, with axial slice orientation and parameters set as follows: TR = 2340 ms, TE = 24 ms, FA = 90°, no interslice gap, Field of View (FoV) = 224 mm × 224 mm, matrix size = 160 × 160 × 86, and voxel size of (1.4 × 1.4 × 1.4) mm^3. The first three scans were discarded to reduce saturation effects. To control for physiological noise in the fMRI data, participants' pulse and respiration were recorded using a pulse oximeter and a breathing belt (Siemens Healthineers, Erlangen, Germany). Following the fMRI scan, a 2D GRE field mapping sequence was performed to evaluate B0 magnetic field inhomogeneity. The acquisition parameters for the field mapping were as follows: 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, with a total acquisition time of 1:38 minutes. For anatomical reference, a high-resolution T1-weighted image was captured using a Magnetization-Prepared with 2 RApid Gradient Echoes (MP2RAGE) sequence, with parameters including TR = 4300 ms, TE = 1.98 ms, FA = 5°/6°, TI = 940 ms/2830 ms, bandwidth of 240 Hz, matrix size = 256 × 256 × 224, acceleration factor = 3, and voxel size of (0.75 × 0.75 × 0.75) mm^3.

Data Preprocessing

MP2RAGE images underwent denoising using Statistical Parametric Mapping (SPM12) with a method detailed in (O'Brien et al., 2014). Subsequently, these denoised images were automatically reoriented using SPM and corrected for intensity bias caused by field inhomogeneity using the bias correction method within the SPM's "unified segmentation" approach (Ashburner and Friston, 2005). Brain extraction was performed on the denoised, reoriented, and bias-corrected images to avoid potential co-registration issues arising from the use of dielectric pads during the scans. This process was carried out using Advanced Normalization Tools (ANTs). The fMRI time series preprocessing included: 1) auto-reorientation; 2) realignment and unwarping to correct for head motion and field inhomogeneities; 3) brain extraction, conducted using ANTs to remove non-brain tissue; 4) smoothing applied with a Gaussian kernel (3mm full-width at half maximum) to improve signal-to-noise ratio.

Statistical Analyses

For first-level analysis, each subject's data were analyzed in their native space to minimize errors from co-registration. The whole-brain univariate analyses consisted of a general linear model

(GLM) computed with SPM12. Task and light blocks were modelled as block functions and convolved with the canonical hemodynamic response function. The fMRI time series was high-pass filtered (cutoff = 256 seconds) to remove low- frequency drifts. Movement and physiological parameters (heart rate and respiration), calculated using 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. The primary analysis aimed to assess whether the hypothamus activity during the task were influenced by overall changes in illuminance levels. The task block regressors were accompanied by a single parametric modulation regressor reflecting the light melanopic illuminance levels (0, 0.16, 37, 92, 190 melEDI). The contrasts of interest focused on the main effects of this parametric modulation. In the follow-up post hoc analysis, we evaluated responses to stimuli under each light condition. Separate regressors represented each task level across the different light conditions (0, 0.16, 37, 92, 190 melEDI). The contrasts of interest consisted of the main effects of each regressor.

Using a deep learning approach implemented in FreeSurfer (Billot et al., 2020), we segmented the hypothalamus into five subregions: inferior-anterior, superior-anterior, posterior, inferior-tubular and superior-tubular (**Figure 5-2 A**). We then utilized the output masks from this segmentation to extract regression betas (activity estimates) for each hypothalamic subregion using the REX Toolbox (Duff et al., 2007). Activity estimates were then averaged (mean) within each subpart and across both hemispheres. In the main analyses, this resulted in one activity estimate for each task stimulus type and each hypothalamic subregion (totaling 10 per individual). In the subsequent analyses, we obtained five activity estimates for each task stimulus, light stimulus type and each subregion (total of 50 per individual).

Statistical analyses of hypothalamic activity estimates were conducted using SAS 9.4 (SAS Institute, NC, USA). The analyses employed Generalized Linear Mixed Models (GLMM), incorporating the subject as a random factor for both intercept and slope, and were adjusted for the distribution of the dependent variable. Direct post hoc tests were adjusted for multiple comparisons using the Tukey method. Subsequent detailed analyses were treated as post hoc and did not undergo multiple comparison corrections ($p < 0.05$). To identify outliers in the datasets, Cook's distance greater than 1 was utilized for exclusion. This process revealed two outliers in the activity estimates for each of evening adults, morning adults, and adolescents groups. Semi-partial R^2 ($R^2\beta^*$) values

were computed to estimate the effect sizes of significant fixed effects and statistical trends in all GLMMs (Jaeger et al., 2017).

The primary analyses focused on activity estimates modulated by light illuminance, as the dependent variable. The hypothalamic subpart and task stimulus type (2- back/0-back) were included as repeated measures, with age, sex, BMI, and season serving as covariates, along with an interaction term between task stimulus type and hypothalamic subpart.

The subsequent set of post hoc GLMM analyses examined the activity estimates of the hypothalamic subparts as the dependent variable, and hypothalamic subpart, task stimulus type, and illuminance levels (0, 0.16, 37, 92, 190 melEDI lux) as repeated measures, with age, sex, BMI, and season as covariates, along with an interaction term for illuminance and hypothalamic subpart. When investigating the effects of time-of-day and age group, these variables were included in separate GLMM models as interactions with activity estimates modulated by light illuminance and/or illuminance levels.

Results

Forty-nine healthy participants were included in the analyses: 18 young adults scanned in the morning (12 women, 24.0±2.4 y), 15 young adults scanned in the evening (8 women, 24.6±3.8 y) and 16 adolescents scanned in the evening (5 women, 16.75±1.1 y). Participants completed an auditory executive task (n-back (Collette et al., 2005)) while undergoing high-resolution 7-Tesla functional MRI scan. During the scan, they were alternatively maintained in darkness or exposed to four different light illuminance levels (0.16, 37, 92, and 190 melEDI lux) for short intervals (30-70 sec). The hypothalamus was parcellated into five subparts, inferior-anterior, superior-anterior, posterior, inferior-tubular and superior- tubular (**Figure 5-2 A**), which covered most of the hypothalamus, so brain activity estimates could be consistently extracted from each of these subparts in each participant.

Similar Regional Impact of Illuminance on Hypothalamus Activity between the Morning and the Evening

Our primary analysis regarding time-of-day aimed to detect differences in the overall effects of illuminance changes across the five distinct hypothalamic subparts between the participants recorded in the morning vs. those recorded in the evening. For each subpart, an index was computed to reflect the influence of illuminance, derived from the average brain activity estimates

that captured how task-related neural activity was modulated by changes in illuminance. As in our previous publication only comprising morning recordings, the statistical analyses, with the activity of each subparts as dependent variable, yielded significant differences between the subparts (GLMM; main effect of hypothalamus subpart: $p<0.0001$), indicating that each subpart responded differently to changes in light levels (**Table 5-2**). Importantly, however, the analyses did not reveal any time-of-day nor time-of-day by hypothalamus subpart interaction ($p > 0.59$), supporting that the impact of light was similar in the morning and in the evening. We further observed a statistical trend for main effects of task ($p = 0.08$), and a main effect of age ($p = 0.04$), while no significant effects were found for the other covariates.

Again, similarly to our previous publication with morning recordings, the post hoc contrasts showed that the effect of illuminance variation was consistently higher in the posterior hypothalamus when compared to the other subparts ($p \leq 0.0006$), which did not significantly differ from one another (**Figure 5-2 B, Table 5-2**). In addition, as indicated by the absence of main effect for time-of-day, none of the subparts was significantly different in the morning vs. the evening (**Figure 5-2 C**). When considering the impact of illuminance in both groups separately, post hoc contrasts further indicated the modulation of the activity of the posterior hypothalamus by the overall changes in illuminance was significantly higher ($p_{corrected} < 0.05$) from the other 4 subparts in the morning group, while it was higher than the superior-anterior and inferior-anterior subparts in the evening (**Figure 5-2 C, Table 5-2**). Finally, given the significant difference in chronotype between morning and evening participants, we included chronotype as an additional covariate, but it had no impact on the outcomes of the statistical model (and chronotype was not significantly associated to the activity of the hypothalamus subparts; $p = 0.32$).

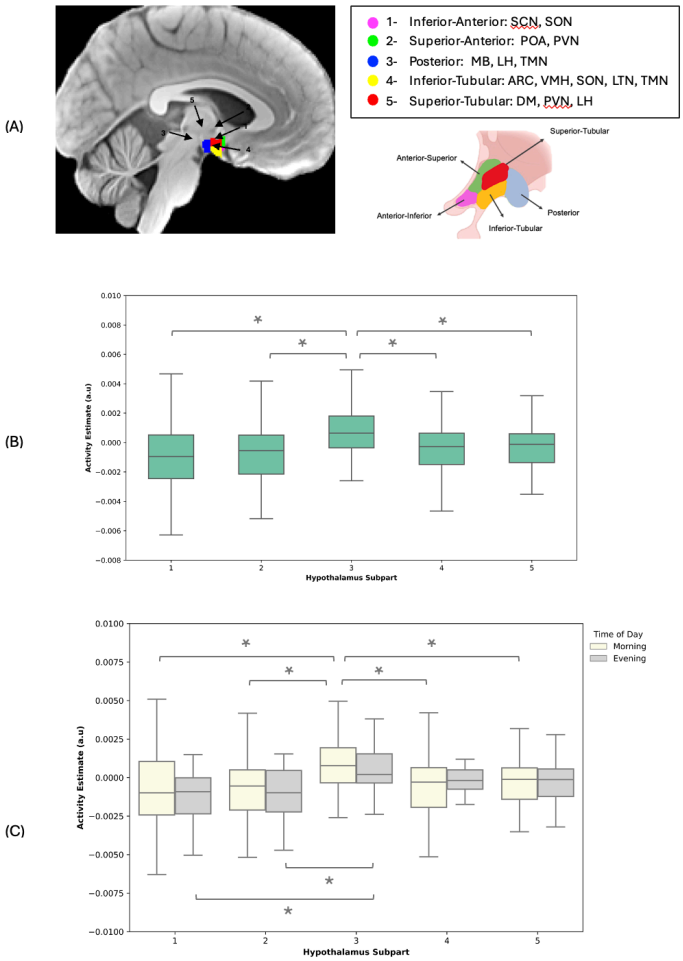


Figure 5-2: Segmentation of the hypothalamus into five subparts & hypothalamic response to light in adults and at different times of day.

(A)The nuclei encompassed by different subparts are indicated in the right inset. 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) Activity estimates (beta; arbitrary unit – a.u.) of the collective impact of illuminance variation on the activity of each hypothalamus subpart (Morning and evening subject together). (C) Group comparison of activity estimates of the collective impact of illuminance variation on each hypothalamus subpart in the morning vs. in the evening. Box plots show the median and interquartile range, representing the 25th to 75th percentile. Asterisks (*) denote significant differences.

Table 5-2: Statistical outputs of GLMM analysis for regional hypothalamic response in adults. Differences between hypothalamus subparts in response to variation in illuminance along with outputs of the post-hoc test for pairwise comparison of hypothalamus subparts.

MAIN GLMM

Effect	F-value	P-value	Partial R^2
Hypothalamus subpart	10.82	**<0.0001**	**0.14**
Time	0.04	0.84	
Hypothalamus subpart × Time	0.70	0.59	
Task	3.20	0.08	
Age	4.34	**0.04**	**0.09**
Sex	1.72	0.20	
BMI	0.57	0.45	
Season	1.65	0.21	

***POST-HOC*: PAIRWISE COMPARISON OF HYPOTHALAMUS SUBPARTS**

Contrast	T-value	$P_{uncorrected}$	$P_{corrected(Tukey)}$
1 vs. 2	-0.67	0.50	0.96
1 vs. 3	-5.92	**<.0001**	**<.0001**
1 vs. 4	-1.31	0.19	0.68
1 vs. 5	-1.87	0.06	0.33
2 vs. 3	-5.26	**<.0001**	**<.0001**
2 vs. 4	-0.64	0.52	0.97
2 vs. 5	-1.20	0.23	0.75
3 vs. 4	4.61	**<.0001**	**<.0001**
3 vs. 5	4.05	**<.0001**	**0.0006**
4 vs. 5	-0.56	0.58	0.98

***POST-HOC*: PAIRWISE COMPARISON OF HYPOTHALAMUS SUBPARTS IN THE MORNING AND IN THE EVENING**

Contrast	Morning		Evening	
	T-value	$P_{corrected(Tukey)}$	T-value	$P_{corrected(Tukey)}$
1 vs. 2	0.10	1.0	-1.03	0.84
1 vs. 3	**-4.30**	**0.0002**	**-4.08**	**0.0006**
1 vs. 4	-0.19	1.0	-1.65	0.47
1 vs. 5	-0.50	0.99	-2.13	0.21
2 vs. 3	**-4.40**	**0.0002**	**-3.05**	**0.02**
2 vs. 4	-0.28	1.0	-0.62	0.97
2 vs. 5	-0.60	0.98	-1.10	0.81
3 vs. 4	**4.12**	**0.0005**	2.43	0.11
3 vs. 5	**3.80**	**0.002**	1.95	0.29
4 vs. 5	-0.31	1.0	-0.48	0.99

Opposite Response to illuminance in the Posterior and Anterior/Inferior Hypothalamus

We further investigated the differences in hypothalamic activity across different subparts, by examining the responses of each subpart at different illuminance levels. As in our previous publication, on top of a main effect of illuminance ($p = 0.0003$), the statistical analysis confirmed that the activity dynamics across illuminance levels differed between the five subparts during the executive task (GLMM; Hypothalamus subpart-by-illuminance interaction; $p = 0.0013$) (**Table 5-3**). As in our main analysis, there were no main effects of time-of-day or interaction terms with time-of-day, further supporting that the impact of illuminance on the hypothalamus subparts was similar in the morning and in the evening.

Table 5-3: Statistical outputs of GLMM analysis for the reponse of hypothalamus subparts to each illuminance level at different times of day.

MAIN GLMM

Effect	F-value	P-value	Partial R^2
Illuminance	5.34	**0.0003**	**0.02**
Hypothalamus subpart	1.32	0.26	
Hypothalamus subpart × Illuminance	2.42	**0.0013**	**0.03**
Time	0.74	0.40	
Time × Illuminance	0.38	0.83	
Time × Hypothalamus subpart	2.10	0.08	0.02
Time × Hypothalamus subpart × Illuminance	0.59	0.90	
Task	3.46	0.06	0.01
Age	7.08	**0.01**	**0.17**
Sex	0.38	0.54	
BMI	0.10	0.75	
Season	3.17	0.09	0.10

Post hoc analyses were conducted to evaluate the impact of illuminance within each subpart (**Figure 5-3; Suppl. Table 9-8**). The posterior hypothalamus exhibited increased activity at the two highest illuminance levels (92 and 190 melEDI) compared to darkness ($p = 0.016$ and $p = 0.005$, respectively). In contrast, the inferior-anterior and superior-anterior hypothalamus showed a significant decrease in activity ($p < 0.05$) under all blue-enriched conditions (37, 92, and 190 melEDI) compared to darkness. Moreover, the inferior-tubular subregion showed reduced activity at the highest illuminance level (190 melEDI) compared to the low illuminance conditions (0 and

0.16 melEDI) ($p<0.05$), and also exhibited decreased activity under the two other blue-enriched light conditions (37 and 92 melEDI) compared to darkness. In contrast, the superior-tubular subpart did not show any significant changes in activity with varying illuminance levels. When examining the morning and evening groups separately, we observed similar patterns of activity across both groups: the posterior hypothalamus showed a clear increase in activity with higher illuminance, while the inferior-anterior, superior-anterior, and inferior-tubular subparts all exhibited a decrease in activity. In contrast, the superior-tubular subpart remained largely unaffected, showing no significant change across the varying illuminance levels (**Figure 5-3**).

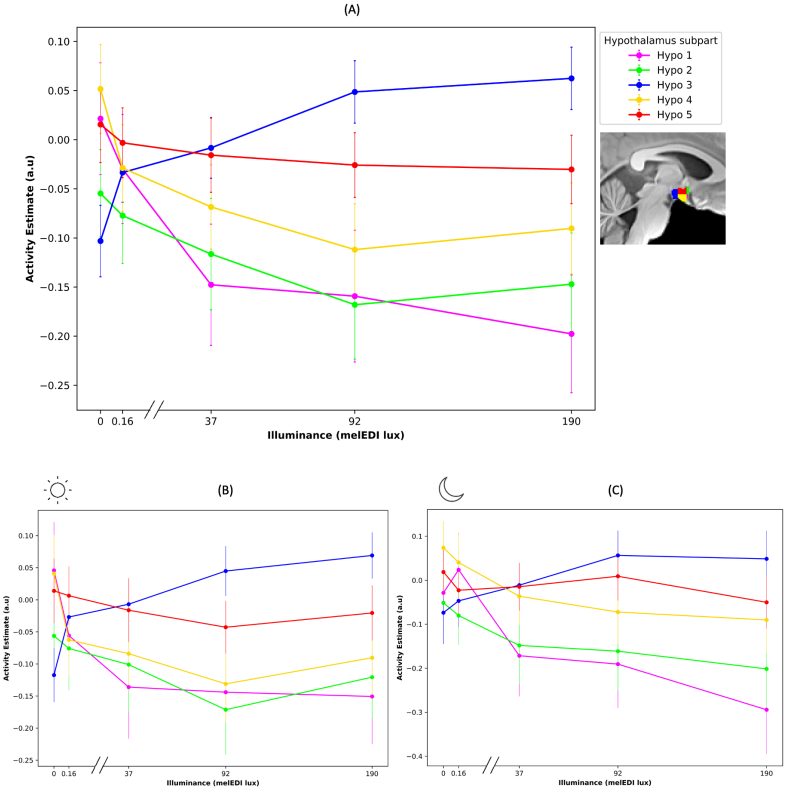


Figure 5-3: Activity dynamics across illuminance for each subpart.
Morning and evening groups together (A). Morning group (B) and evening group (C) separately.

Adolescents Exhibit different Hypothalamic Response to Illuminance, over the Anterior and Tubular Subparts

Our second primary analysis focused on developmental stage. We aimed to investigate whether the regional response of the hypothalamus to light differed between adolescents and young adults. Given the concerns about evening light exposure in adolescents, data were collected approximately one hour before their habitual bedtime and group comparisons were therefore made only for evening light exposures.

As in the first primary analysis, the GLMM yielded a main effect of hypothalamus subpart ($p<0.0001$), but no significant effect of age group, nor age group by hypothalamus subpart interaction ($p > 0.5$). (**Table 5-4**). Post hoc contrasts further confirmed that in young adults the modulation of the activity of the posterior hypothalamus by the overall changes in illuminance was significantly higher ($p_{corrected} < 0.05$) than in the other 4 subparts, which did not differ significantly from one another (**Table 5-4**). In adolescents, the modulation of activity in the posterior subpart by illuminance was significantly higher ($p_{corrected} < 0.05$) compared to the superior-anterior and inferior-anterior subparts. Overall, this analysis suggests that the linear effect of changes in illuminance is similar across both age groups. However, this does not mean that there are no local non-linear differences in some subparts. To investigate this further, we examined the activity of different hypothalamic subparts at each level of illuminance.

Table 5-4: Statistical outputs of GLMM analysis for the reponse of hypothalamus subparts in different age groups.

MAIN GLMM

Effect	F-value	P-value	Partial R^2
Hypothalamus subpart	10.73	**<0.0001**	**0.15**
Age Group	0.45	0.51	
Hypothalamus subpart × Age Group	0.76	0.55	
Task	0.03	0.87	
Sex	0.36	0.55	
BMI	0.54	0.47	
Season	0.13	0.72	

***POST-HOC*: PAIRWISE COMPARISONS OF HYPOTHALAMUS SUBPARTS IN YOUNG ADULTS AND IN ADOLESCENTS**

Contrast	Young Adults		Adolescents	
	T-value	$P_{corrected(Tukey)}$	T-value	$P_{corrected(Tukey)}$
1 vs. 2	-0.50	0.99	0.05	1.00
1 vs. 3	**-5.52**	**<.0001**	**-2.89**	**0.03**
1 vs. 4	-2.00	0.27	-1.21	0.75
1 vs. 5	-2.46	0.10	-1.77	0.39
2 vs. 3	**-4.71**	**<.0001**	**-2.94**	**0.03**
2 vs. 4	-1.49	0.57	-1.26	0.72
2 vs. 5	-1.96	0.29	-1.82	0.36
3 vs. 4	**3.22**	**0.01**	1.68	0.45
3 vs. 5	**2.76**	**0.04**	1.12	0.80
4 vs. 5	-0.46	0.99	-0.56	0.98

The GLMM using the activity of each subpart under each illuminance as dependent variable, first confirmed distinct changes in activity across subparts under different illuminance levels (subpart-by-illuminance interaction: p=0.0001), along with the main effects of illuminance ($p < 0.0001$), and task ($p = 0.01$). Critically, the GLMM revealed a significant interaction between illuminance and age group ($p < 0.0001$) indicating that changes in overall hypothalamus activity with variations in illuminance was distinct between adolescents and young adults.

Post hoc analyses indicated that at the highest illuminance level (190 melEDI), overall hypothalamic activity differed significantly between the two age groups , with adolescents showing lower activity compared to young adults (**Figure 5-4 A; Table 5-5**). This difference was largely

attributed to the superior-anterior (p = 0.04) and inferior-tubular (p = 0.04) subparts, which showed greater deactivation in adolescents in response to the highest illuminance compared to young adults (**Figure 5-4 B, Suppl. Table 9-9**). Considering the activity of each subpart in each group (**Figure 5-4 C**) we noted that the inferior-anterior subpart shows a significant decrease in activity with increasing illuminance in both groups. In contrast the posterior subpart showed a significant increase only in young adults while the superior-anterior and inferior-tubular showed a significant decrease only in teenagers. Therefore, except for the inferior-anterior subpart, the other subparts displayed distinct dynamics in each groups that reach significance as between group difference in the superior-anterior and inferior-tubular subparts (**Suppl. Table 9-10**).

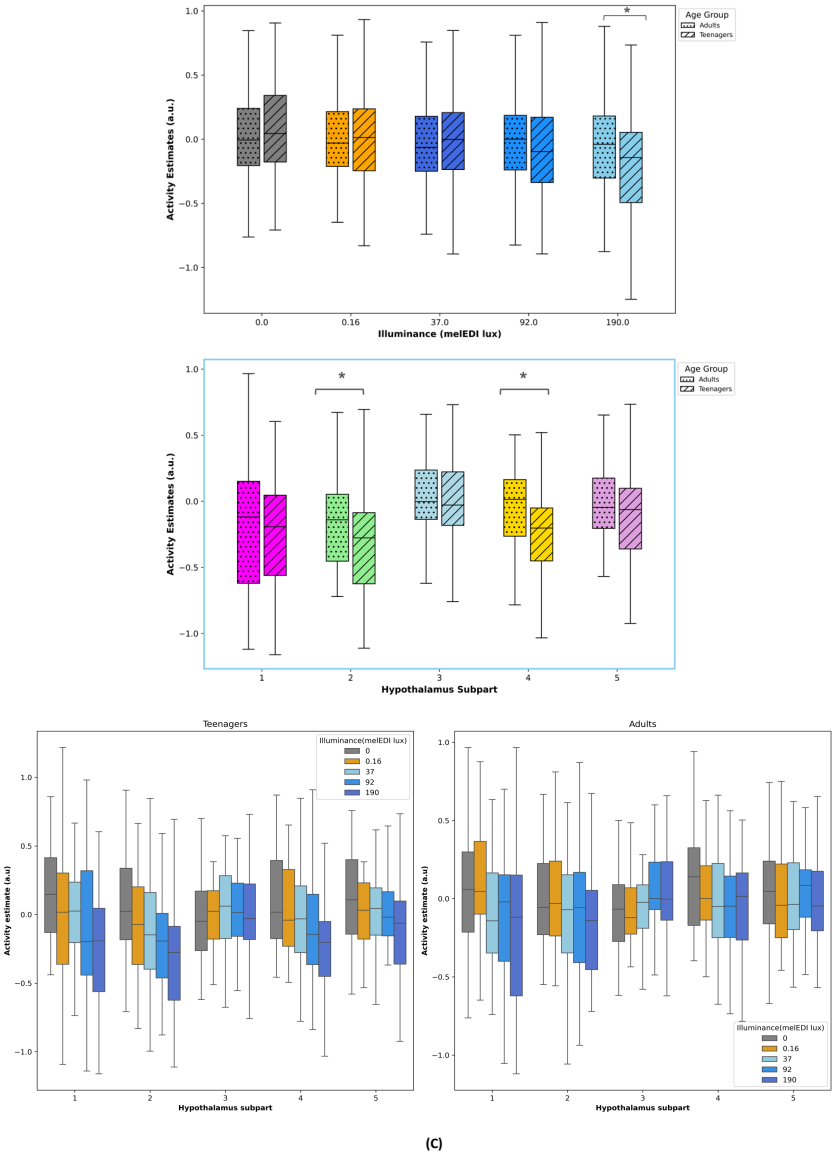
Table 5-5: Statistical outputs of GLMM analysis for the reponse of hypothalamus subparts to each illuminance level in different age groups.

MAIN GLMM

Effect	F-value	P-value	Partial R^2
Illuminance	13.35	**<.0001**	**0.04**
Hypothalamus subpart	1.89	0.11	
Hypothalamus subpart × Illuminance	2.88	**0.0001**	**0.04**
Age group	0.01	0.92	
Age group × Illuminance	5.98	**<.0001**	**0.02**
Age group × Hypothalamus subpart	0.81	0.52	
Age group × Hypothalamus subpart × Illuminance	0.44	0.97	
Task	6.51	**0.01**	**0.02**
Sex	1.47	0.24	
BMI	2.74	0.11	
Season	0.33	0.57	

GROUP COMPARISON BETWEEN OVERALL HYPOTHALAMUS RESPONSE IN ADOLESCENTS AND YOUNG ADULTS AT DIFFERENT ILLUMINANCE LEVELS

Illuminance	Contrast	T-value	$P_{corrected(Tukey)}$
0	Adolescents vs Adults	1.27	0.20
0.16	Adolescents vs Adults	-0.09	0.93
37	Adolescents vs Adults	0.92	0.36
92	Adolescents vs Adults	-0.54	0.59
190	Adolescents vs Adults	**-1.97**	**0.04**



(C)

Figure 5-4: Group comparison of hypothalamic response between adolescents and adults.
Overall response of hypothalamus to each illuminance level (A). Group comparison of the response of each hypothamus subpart at 190 melEDI lux (B). Response of each hypothalamus subpart to each illuminance in adolescents (left) and young adults (right) (C).

Discussion

The precise brain wiring of the biological impact of light on NIF brain function is not established, particularly in humans where translations of the findings in animal remain scarce. Here, we focused on the hypothalamus, as it is the primary brain region receiving most of the outputs from ipRGCs. In this study, we examined whether the impact of changes in illuminance on the regional activity of hypothalamic subparts was influenced by the time-of-day (morning vs. evening) and developmental stage (adolescents vs. young adults). This extends our previous investigation, which found an anterior-posterior gradient in the impact of illuminance across the hypothalamus when exposed to light in the morning (Campbell et al., 2024b). Our results reveal that the anterior-posterior gradient in the impact of illuminance is similarly present in the evening with the posterior hypothalamus showing increased activity as illuminance rises, while the anterior part exhibits a decrease. Although the overall gradient also appears similar in both adolescents and young adults, a more detailed analysis showed distinct dynamics, particularly within the superior-anterior and inferior-tubular subparts in adolescents, which showed a significantly greater decrease in activity as illuminance increased compared to young adults. These results indicate that the previously reported time-of-day difference in the impact of light on brain activity and performance (Vandewalle et al., 2011a) are not primarily driven by a prominent difference in the hypothalamus. In contrast, the previous reports that evening light may affect the circadian system and behavior in adolescents differently (Eto and Higuchi, 2023) may be at least in part grounded onto regional difference in the response to light across hypothalamus subparts. These findings will contribute to a deeper understanding of the biological effects of light on the brain and offer insights for developing more personalized light interventions.

As in our initial study (Campbell et al., 2024b), despite employing a standardized, reproducible procedure to parcellate the hypothalamus into subparts (Billot et al., 2020) and using ultra-high-field MRI, achieving precise resolution of individual hypothalamic nuclei in humans remains unattainable. This is primarily due to the low contrast between the nuclei, as highlighted in previous work (Sharifpour et al., 2022a).

This limitation prevents us from attributing our findings to a specific nucleus and we can only suggest a variety of potential interpretations that would require further investigation. Since we did not observe any time-of-day differences, the interpretations we proposed for the regional impact of illuminance across the hypothalamus in the morning still apply to the evening. We briefly summarize these interpretations in the following lines. The posterior hypothalamus subpart

encompasses part of the LH and the TMN, which respectively produce orexin and histamine—both known to promote wakefulness—and animal histology has shown direct projections from ipRGCs to the LH (Do, 2019; Hattar et al., 2006; Scammell et al., 2017). Light may enhance wakefulness by activating these wake-promoting circuits, possibly through an elevated release of orexin and histamine both in the morning and in the evening. This aligns with previous research linking light exposure to improved alertness and reduced subjective sleepiness in the evening (Campbell et al., 2023). Orexin is a good candidate to constitute the circadian signal that promotes wakefulness (Zeitzer, 2013). If we are indeed facing a change in LH activity with increasing illuminance, this could mean that light similarly induces orexinergic signaling to promote wakefulness both in the morning, shortly after waking, and in the evening, around habitual sleep time.

Similarly, the anterior and tubular subparts of the hypothalamus encompass several nuclei, including two key projection sites of ipRGCs: the SCN and VLPO, which are involved, respectively, in circadian and sleep regulation (Porcu et al., 2018), as well as part of the TMN (Zhang et al., 2021). Decreased activity we found in these subparts may reflect a reduction in GABAergic signaling from either of these nuclei (Albers et al., 2017; Chung et al., 2017; Scammell et al., 2019), potentially relieving inhibition on their downstream targets and promoting wakefulness. Regardless of the precise signaling mechanisms, the decreased activity we observed in the anterior hypothalamus during the day (Campbell et al., 2024b; Schoonderwoerd et al., 2022) appears to be consistent in the evening. This is reminiscent of a previous positron emission tomography (PET) study that reported decreased glucose uptake in the anterior hypothalamus following light exposure at night (Perrin et al., 2004).

Interestingly, VLPO was suggested to deliver inhibitory GABAergic and galaninergic inputs to neurons of the TMN, as well as other components of the ascending monoaminergic arousal system (Arrigoni and Fuller, 2022). Therefore, the opposite activation patterns observed in the anterior region (which includes the VLPO) and the posterior region (which includes the TMN) may be in line with this assumption.

Our findings, which reveal that the impact of light on hypothalamic activity extends into the evening as well as the morning, highlight the importance of carefully managing evening light exposure. The observation of similar effects in the evening raises concerns about the potential disruptive effects of high illuminance levels, especially those exceeding the recommended maximum of 10 melEDI lux for evening light (Brown et al., 2022). Such exposure has been shown to disrupt circadian rhythms and sleep (Chellappa et al., 2013). Broadly speaking, our findings

suggest that the hypothalamus may maintain a level of consistency in processing light stimuli across different times of the day. This would imply that the differential acute biological effects of light on brain function, as reported in previous studies (Vandewalle et al., 2011a), may be mediated through other brain regions, such as the pulvinar in the thalamus (Paparella et al., 2023; Vandewalle et al., 2006) or the locus coeruleus in the brainstem.

When comparing adolescents and young adults, we initially found that the overall impact of illuminance on hypothalamic activity did not differ between the two age groups. While this result may not be surprising, given that light likely affects physiology similarly in individuals between the ages of 15 and 30, more detailed analyses revealed differences that were not captured by the linear regression model used to assess the overall impact of illuminance. Specifically, the dynamics of activity changes induced by variations in illuminance appeared to differ across hypothalamic subparts. One notable exception was the inferior-anterior subpart, which displayed qualitatively similar patterns of activity in both age groups, suggesting that the activity of the SCN (or other nuclei within this subpart) and its impact on downstream targets is unchanged between adolescents and young adults. While we observed some distinct dynamics in the posterior hypothalamic subpart between the two groups, the differences were not statistically significant, so we will not discuss them further.

In contrast, the superior-anterior and inferior-tubular subparts of the hypothalamus exhibited a sharper decrease in activity in response to higher light levels, with a more pronounced decrease in adolescents compared to young adults. This stronger response in adolescents appeared to drive the highest illuminance-induced difference in hypothalamic activity between age groups, irrespective of hypothalamic subpart, as indicated by the significant interaction between illuminance and age group.

Adolescents may therefore exhibit a stronger response to changes in illuminance, at least in some parts of the hypothalamus, compared to young adults. This could contribute to concerns around evening light exposure in this age group, which could be more sensitive to light due to factors such as larger pupil size, clearer lens, and/or a later chronotype (Eto et al., 2021; Eto and Higuchi, 2023; MacLachlan and Howland, 2002; Wright et al., 2013). This age- related difference in hypothalamic response might also arise from ongoing neurodevelopmental changes that can potentially alter neurotransmitter dynamics, or the density and connectivity of neural circuits involved in inhibitory responses to light.

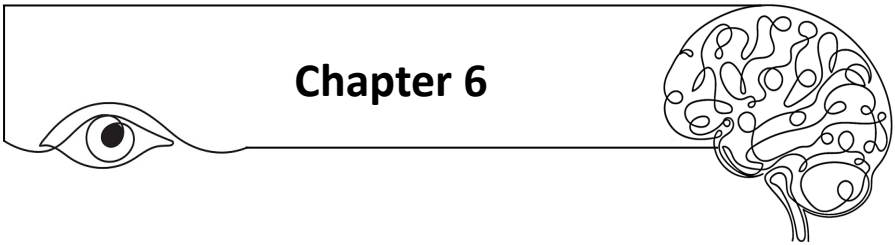
If we keep similar interpretation as for adults in terms of the precise hypothalamus nuclei that may be involved, the age-group difference we detect over the superior-anterior subpart of the hypothalamus could correspond to a stronger response of the VLPO or preoptic area, and, given their important role in sleep regulation (Arrigoni and Fuller, 2022; Scammell et al., 2017), contribute to sleep disturbances. Likewise, the inferior-tubular subpart could correspond part of the TMN and imply a reduced GABAergic (or histaminergic) output of the nuclei that could disturb downstream sleep regulation. We stress; however, a recent study has reported that while adolescents show a greater melatonin suppression by light, their recovery is faster compared to adults (Höhn et al., 2024). Specifically, it was shown that once the light was turned off, the melatonin suppressed by light exposure returned to its pre-exposure level within about 50 minutes in adolescents. This suggest that although adolescents may experience a stronger acute impact from light exposure, potentially through the specific impacts we detected in the hypothalamus, the effects may dissipate more quickly than in younger adults, indicating that young adults could actually be more susceptible to NIF effects.

As in any research, our study bears limitations. The primary limitation is the between-group design, as opposed to a within-subject design, which would have imposed a much higher workload and risk of dropout. Coupled with our relatively small sample size within each group, this may have reduced the statistical power of our analyses, meaning there could be weaker effects that we were unable to detect. Additionally, data collection in adolescents was not conducted in the morning, due to concerns about school schedules dropout rates, which may have impacted our ability to capture the full range of potential effects. Furthermore, we used short light exposures, which may produce different results compared to longer light exposures, especially in relation to hypothalamus activity. Another limitation is that, while in our previous study we observed an effect of light on performance in the 2- back task in the morning, linked to activity changes in the posterior hypothalamus (though negatively correlated), behavioral data in this study could not (yet) be fully analyzed and related to hypothalamic activity differences. Further analyses of these behavioral data are warranted to better understand the relationship between light exposure, hypothalamic activity, and performance.

In conclusion, this study contributes to the growing body of literature on the relationship between environmental light exposure and an important brain structure, i.e. hypothalamus, and provides important insights into the differential effects of illuminance on hypothalamic activity across different subparts, times of day, and developmental stages. The posterior hypothalamus seems a

key region in mediating the arousing effects of light, whereas the anterior hypothalamus seems to contribute to the alerting effects of light by inhibiting sleep-promoting circuits, especially in the evening. In adolescents, we observed a stronger response to light in the evening, particularly in subparts of the hypothalamus involved in sleep regulation. This reinforces concerns about the disruptive effects of evening light on sleep in this age group and highlights the need for careful management of light exposure during this key developmental period.

These findings may have important implications for optimizing light exposure to regulate sleep and wakefulness, as well as for enhancing lighting environments in settings like schools, workplaces, and therapeutic spaces.



Chapter 6

Light Impact on Thalamo-Cortical Connectivity During an Executive Cognitive Task: Effects of Time of Day and Specificities of Teenagers

This chapter is based on our submitted paper:

Sharifpour, R., Campbell, I., Paparella I., Balda, F., Beckers, E., Read, J., Mortazavi, N., Koshmanova, E., Zubkov, M., Talwar, P., Collette, F., Phillips, C., Lamalle, L., Vandewalle, G. (2024)

Abstract

Light affects more than just vision; it impacts attention, alertness and cognition. These non-image forming (NIF) effects are primarily mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs), which project widely to the brain and are maximally sensitive to short-wavelength blue light. While human imaging studies have demonstrated that light influences regional brain activity in both subcortical and cortical areas, how it affects the crosstalk between brain regions is not fully understood. Building on previous research, we examined how light affects thalamo-cortical connectivity during an auditory executive task. Fifty-five participants including 37 adults (19-30y; 20 scanned in the morning and 17 in the evening) and 18 adolescents (15-18y; scanned in the evening), underwent 7-Tesla functional magnetic resonance imaging (7T fMRI) to investigate the modulatory impact of illuminance on effective connectivity within a thalamo-cortical network crucial for executive functioning, particularly working memory. This network composed of the mediodorsal nucleus of the thalamus (MDN), the supramarginal gyrus (SMG), and the inferior frontal junction (IFJ). We found that moderate illuminance blue-enriched light (92 melanopic Equivalent Daytime Illuminance – melEDI lux) strengthened the cortico-cortical connectivity from the SMG to IFJ across all groups. Interestingly, low illuminance orange light (0.16 melEDI) also strengthened the thalamus-to-SMG connectivity. Additionally, higher illuminance blue-enriched light (190 melEDI) strengthened the thalamus-to-IFJ connectivity in the morning in young adults, while moderate illuminance (92 melEDI) strengthened the thalamus-to-SMG connectivity in the evening in adolescents. Overall, these results reinforce the view that the thalamus plays a central role in mediating the acute effects of light on cognitive brain function. Our findings confirm that light influences thalamus-to-cortex connectivity to modulate higher-order cognitive functions. This impact appears to vary depending on the time-of-day and age. These insights could inform the development of lighting interventions aimed at optimizing cognitive performance across different age groups and times of day.

Introduction

Light influences not only the visual system but also non-visual functions, such as physiological, hormonal, and neurobehavioral responses (Brown et al., 2022; Campbell et al., 2023; Mahoney and Schmidt, 2024). These non-image forming (NIF) effects are primarily mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs), a third type of photoreceptors in the retina, on top of rods and cones, that are most sensitive to short-wavelength (blue) light at around 480 nm

(Schmidt et al., 2011). IpRGCs directly project to a wide range of brain structures including the hypothalamus, thalamus, and amygdala (check e.g. ref (Campbell et al., 2023) for a review of these projections). Through these widespread projections, light exposure has direct and indirect effects on the regulation of circadian rhythms, sleep-wake cycles and mood, as well as on emotions, attention, alertness and cognitive function (Alkozei et al., 2016a; LeGates et al., 2012; Zhang et al., 2021).

The NIF effects of light are modulated by several factors, including time-of-day, with evidence from human brain studies suggesting stronger effects in the morning than in the evening (Vandewalle et al., 2011a). These effects also vary across lifespan (Chellappa et al., 2021a; Eto and Higuchi, 2023). In particular, research indicates that adolescents may respond more strongly to light than adults (Eto and Higuchi, 2023).

Several human functional magnetic resonance imaging (fMRI) studies showed that, depending on the cognitive task being performed, light can modulate blood oxygen level dependent (BOLD) signals in various cortical and subcortical regions, thereby influencing cognition and performance (Alkozei et al., 2016b; Vandewalle et al., 2007a, 2006) (for a comprehensive review, see ref (Campbell et al., 2023)). However, the neural mechanisms and modulating factors by which light affects cognition are not yet fully understood. We previously hypothesized that the influence of light on cognition and performance might be mediated by changes in brain connectivity, particularly from subcortical structures to the cortical regions engaged in the ongoing cognitive task. The thalamus, a crucial subcortical relay center that interfaces notably between arousal and cognition (Saalmann et al., 2012) is proposed to play an essential role in how light influences information processing in the brain during non-visual cognitive tasks, as evidenced by fMRI studies showing thalamic activation in response to light during cognitive performance (Vandewalle et al., 2007b, 2007a, 2006). In support of our hypothesis, we recently showed that during an attentional task, light influences the connectivity from the thalamus (pulvinar) to intra-parietal sulcus (IPS), key regions to attentional regulation (Paparella et al., 2023). Whether and how these observations extend to other cognitive domains is not known.

Here, we used 7T fMRI to examined how light influences the effective connectivity within a three-region network that plays crucial roles in various cognitive processes, particularly executive functions like working memory, comprising the mediodorsal nucleus of thalamus (MDN), the supramarginal gyrus (SMG), in the immediate vicinity of the IPS, and the inferior frontal junction (IFJ), next to the middle frontal gyrus (MFG) (Deschamps et al., 2014; Sundermann and Pfleiderer, 2012; Wolff and Halassa, 2024). We also examined how different times of the day, and distinct age

groups, particularly adolescents vs. young adults, affect the connectivity among these 3 regions. We hypothesized that blue light would influence the network, particularly thalamo-cortical connectivity, more effectively in the morning compared to the evening, and in adolescents compared to adults.

Material and Method

This study is part of a larger study that has resulted in several publications using different participant subsets (Beckers et al., 2024; Campbell et al., 2024b, 2024a; Paparella et al., 2023). The study was approved by the Ethics Committee of the University of Liège. Participants provided their written informed consent and received financial compensation.

Participants

Between December 2020, and September 2023, a total of 55 healthy volunteers aged 15 to 30 years (22.0±4.6y, 29 Females) participated in the study. This included 18 adolescents (16.7±1.1y, 6 Females) and 37 young adults (24.6±3.3y, 23 Females). Exclusion criteria included a body mass index (BMI) > 28; recent psychiatric history, severe trauma, sleep disorders; addiction, chronic medication; smoking, excessive alcohol consumption (>14 units per week) or caffeinated drinks (>4 cups per day); night shift work within the past year; transmeridian travel in the past 2 months; and a history of ophthalmic disorders. Participants also completed questionnaires assessing anxiety (21-item Beck Anxiety Inventory) (Morin et al., 1999), mood (21-item Beck Depression Inventory-II) (Beck et al., 1988), sleep quality (Pittsburgh Sleep Quality Index) (Buysse et al., 1989), daytime sleepiness (Epworth Sleepiness Scale) (Johns, 1993), insomnia (Insomnia Severity Index) (Morin, 1993), chronotype (Horne-Östberg) (Horne and Ostberg, 1976), and seasonal changes in mood and behavior (Seasonal Pattern Assessment Questionnaire) (Rosenthal, 1984). **Table 6-1** summarizes the demographic characteristics of the participants.

Table 6-1: Demographic characteristics of the participants included in the analyses.

	Adults_Evening (AE)	Adults_Morning (AM)	Adolescents (T)	Comparison (t-test)	
				AE vs AM	AE vs T
Number of Subjects	17	20	18		
Age (mean±SD)	25.2±4.0	24.1±2.5	16.7±1.1	P=0.30	**P<0.0001**
Sex: Female (Male)	10(7)	13(7)	6(12)	P=0.71	P=0.14
Body mass index (kg/m^2)	22.1±2.0	21.3±2.3	21.5±2.5	P=0.30	P=0.42
Depression level (BDI-II[a])	6.6±3.5	6.2±5.5	5.6±4.9	P=0.79	P=0.56
Anxiety Level (BAI[b])	5.1±3.1	5.3±6.1	6.1±6.8	P=0.92	P=0.77
Chronotype (HO[c])	43.1±7.3	51.4±7.6	42.8±7.6	**P=0.003**	P=0.91
Subjective Sleep Quality (PSQI[d])	4.1±1.9	3.7±2.7	4.3±1.6	P=0.63	P=0.77
Habitual daytime Sleepiness (ESS[e])	7.0±2.4	5.9±3.0	6.0±4.2	P=0.33	P=0.50
Insomnia symptoms (ISI[f])	6.2±4.9	4.4±3.4	4.2±5.7	P=0.22	P=0.79
Season of experiment*	-0.43±0.51	-0.14±0.67	-0.36±0.58	P=0.14	P=0.72
Seasonality (SPAQ[g])	1.3±0.9	0.9±0.7	0.7±1.0	P=0.26	P=0.16

[a]. Beck's Depression Inventory II
[b]. Beck's Anxiety Inventory
[c]. Horne and Östberg Questionnaire
[d]. Pittsburg Sleep Quality Index
[e]. EPWORTH Sleepiness Scale
[f]. Insomnia Severity Index
[g]. Seasonal Pattern Assessment Questionnaire
See text for reference of the questionnaires.
* Cosine (acquisition day of year*360/365); 21 December=0°
** All participants in all groups were right-handed.

Protocol and light exposure

Participants followed a loose sleep-wake schedule for seven days before the in-lab experiment (±1h; verified with actigraphy) to prevent excessive sleep deprivation while maintaining realistic conditions. Depending on their fMRI schedule (morning or evening), they arrived at the laboratory either 1.5 hours after waking up or 2 hours before their bedtime. Among adults, 20 out of 37 participated in the morning fMRI session, while the remaining completed the evening session. Due to the general concerns regarding evening light consumption during adolescence, all adolescents completed their fMRI sessions in the evening (we further anticipated that scholar constrains would prevent us from completing fMRI sessions also in the morning).

To control for previous effects of light exposure and have a controlled recent light exposure before the fMRI session, upon arrival, participants first underwent 5 minutes of exposure to high-intensity white light (~1000 lux), followed by 45 minutes of dim light (< 10 lux). During this period, they received instructions for the fMRI study and practiced an executive task (n-back task) on a laptop (**Figure 6-1 A**). Inside the scanner, participants performed an auditory letter variant of the n-back task at two difficulty levels: 0-back and 2-back and responded to the task using an MRI compatible response box. This task involves maintaining and continuously updating relevant information in working memory. In the 0-back task, which is less demanding and serves as a control for baseline brain activity, participants responded whenever the current letter matched a predefined letter. In the more challenging 2-back task, participants determined if the current letter was identical to the one presented two stimuli earlier. We used a block design with stimuli presented in 38 blocks, each lasting approximately 30 seconds, comprising 19 blocks of the 2-back task. The order of the 0-back and 2-back tasks was pseudo-randomized over the entire session.

Participants were alternately maintained in darkness (<0.01 lux) or exposed to blue-enriched cool polychromatic light (6500K) at varying illuminance levels (37, 92, 190 melanopic equivalent daylight illuminance (melEDI) lux), or a control monochromatic orange light (590 nm; 0.16 melEDI lux), to which ipRGCs are nearly insensitive (**Figure 6-1 B**). The detailed methodology for the light set-up and its delivery into the MRI scanner can be found in our previous publications (Paparella et al., 2023). There were 8 blocks per light condition and 6 blocks for the darkness condition. There were also darkness periods (~10 seconds, <0.01 lux) without task between blocks with different light conditions to ensure that the light exposure in one block did not affect brain activity in the subsequent block. During all fMRI sessions, pupil size was measured simultaneously with an eye-tracking device (EyeLink 1000Plus, SR-Research, Ottawa Canada). Eye tracking confirmed that

participants kept their eyes open during the scan. The entire experiment was designed using OpenSesame (3.2.8) (Mathôt et al., 2012).

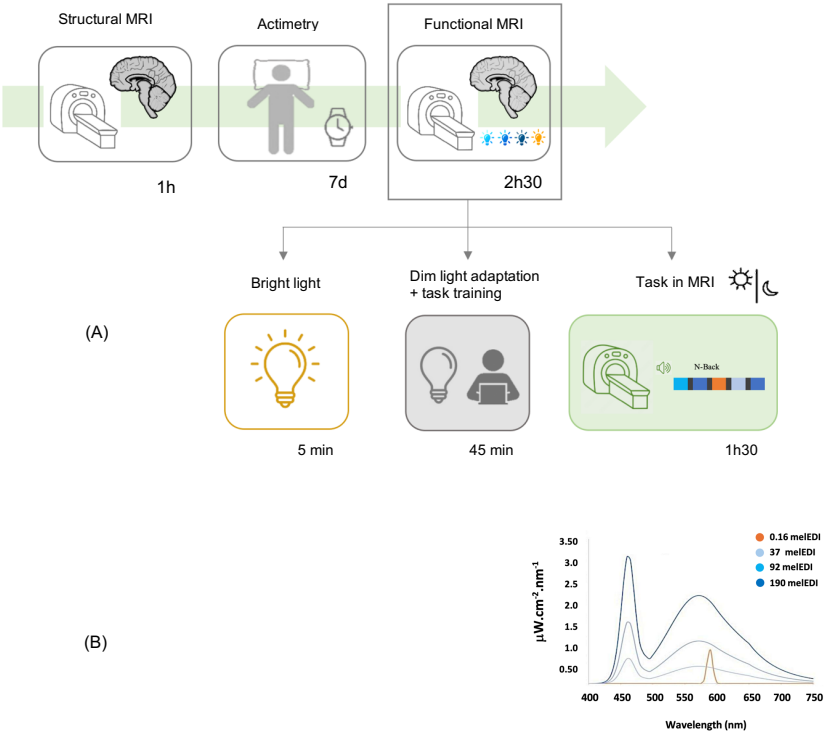


Figure 6-1: Graphical representation of the experimental protocol (A).
The spectrum of the 4 light conditions to which participants were exposed during the n-back task (B).

MRI Data Acquisition

Structural and functional MRI data were acquired using a MAGNETOM Terra 7 Tesla MRI system (Siemens Healthineers, Erlangen, Germany) with a one-channel transmitter, and a 32-channel receiver head coil (Nova Medical, MA, USA). To reduce dielectric artifacts, dielectric pads (Multiwave imaging, Marseille, France) were placed between the head of the participants and the receiver coil. Multi-band Gradient-Recalled Echo-Echo-Planar Imaging (GRE-EPI) sequence was used for acquiring multislice T2*-weighted functional images, with axial slice orientation and

specific parameters including TR =2340 ms, TE =24 ms, FA =90°, no interslice gap, Field of View (FoV) = 224mm × 224mm, matrix size = 160 × 160 × 86, and voxel size of (1.4 × 1.4 × 1.4)mm^3. The initial three scans were excluded to mitigate saturation effects. Additionally, for anatomical reference, a high-resolution T1-weighted image was acquired using a Magnetization-Prepared with 2 RApid Gradient Echoes (MP2RAGE) sequence, with specific parameters including TR =4300 ms, TE =1.98 ms, FA =5°/6°, TI =940 ms/2830 ms, bandwidth of 240 Hz, matrix size =256x256 x224, acceleration factor =3, and voxel size of 0.75x0.75x0.75 mm^3.

Preprocessing

MP2RAGE images were processed using a Statistical Parametric Mapping (SPM12) extension, relying on a regularization factor to limit the background noise (O'Brien et al., 2014). Subsequently, these denoised images were automatically reoriented using SPM and corrected for intensity bias caused by field inhomogeneity using the bias correction method within the SPM's "unified segmentation" approach (Ashburner and Friston, 2005). Brain extraction was performed on the denoised, reoriented, and bias-corrected images to avoid potential co-registration issues arising from the use of dielectric pads during the scans. This process was performed using Advanced Normalization Tools (ANTs, http://stnava.github.io/ANTs/). The fMRI time series were reoriented and then underwent estimation of static and dynamic susceptibility-induced variance using voxel-displacement maps computed from phase and magnitude images. "Realign & Unwarp" was then applied to the EPI images to correct for head motion and for static and dynamic susceptibility induced variance. Realigned and distortion-corrected EPI images then underwent brain extraction with ANTs, followed by smoothing using a Gaussian kernel with a Full Width at Half Maximum (FWHM) of 3 mm. First-level analysis for each subject was conducted in their native space to prevent potential errors introduced by co-registration. Prior to second-level analysis, contrast maps from first-level analyses were transferred to subject structural space, then to group template space, and ultimately to the MNI space (1×1×1mm^3), with all co-registrations performed using ANTs.

Univariate Analysis

For each subject, changes in brain regional BOLD signal were estimated using a general linear model (GLM). Within the GLM design matrix both levels of the task (0-back and 2-back) were modeled as main regressors, and light was included as a modulatory regressor, reflecting the varying levels of illuminance measured in melEDI lux. These regressors were then convolved with

the canonical hemodynamic response function to generate the predicted BOLD response. Movement parameters, as well as cardiac and respiratory parameters derived using the PhysIO Toolbox (Translational Neuromodeling Unit, ETH Zurich, Switzerland) (Kasper et al., 2017), were included as regressors of no interest in the GLM. To eliminate low-frequency drifts, high-pass filtering was applied with a cut-off frequency of 256 Hz. Our contrast of interest focused on regions showing increased activation in response to the 2-back task compared to the 0-back, independent of light condition. These contrast images (in MNI space) were then taken to the second level analysis, employing a random-effects model to examine group-level effects. To control for multiple comparisons, the results were corrected at the voxel level using a family-wise error (FWE) procedure, with a significance threshold set at 0.05.

Based on the group-level results, group peak coordinates of regions of interest (ROIs) in the left hemisphere were identified: MDN of the thalamus, the SMG, next to the IPS, and the IFJ, next to the MFG (**Figure 6-2 A**). The left hemisphere was picked, as research has demonstrated hemispheric asymmetry in working memory, with the left hemisphere showing greater activation in verbal working memory and the right hemisphere in spatial working memory (Thomason et al., 2009). These ROIs were selected because the prefrontal and parietal cortices are integral to the phonological loops involved in verbal tasks and are typically engaged during the n-back task (Na et al., 2000; Owen et al., 2005; Wang et al., 2019). Additionally, thalamus involvement is commonly reported in the context of working memory (Dagenbach et al., 2001; de Bourbon-Teles et al., 2014). Individual ROIs were then defined by selecting the first activated cluster within a sphere of specific radii, determined based on the size of each nucleus, centered on the group peak coordinates of SMG (8 mm), IFJ (8 mm), and MDN (5 mm). For the effective connectivity analysis, BOLD time series were used to infer the underlying neural activity. The first principal components (eigenvariates) of the BOLD signal time series within those ROIs were extracted from the individual statistical map, which was thresholded at p = 0.05 uncorrected (**Figure 6-2 A**). For the eigenvariate extraction the "adjusted" time series were used, which represents the time series after regressing out effects of no interest, using the approach outlined by Zeidman et al (Zeidman et al., 2019a).

Effective Connectivity Analysis and Statistics

Dynamic Causal Modelling (DCM) framework (Zeidman et al., 2019a), implemented in SPM12, was used to investigate how light modulates effective connectivity among the three ROIs. In the DCM analysis, six inputs were defined within a design matrix and then imported into the DCM framework. These inputs comprised all 0-back and 2-back blocks as two separate driving inputs, as

well as blocks representing the four light conditions (including orange light and blue-enriched cool light at three different melEDI levels), each serving as separate modulatory inputs. The DCM model included all intrinsic connectivity among the three regions, along with self-feedback gain control connectivity. Additionally, the model considered the influence of the task on all regions and allowed for the potential modulation of connectivity between regions by all light conditions (**Figure 6-3 A**). Time series extracted from individual ROIs were subjected to a first-level DCM analysis, where the model was estimated for each subject. Subsequently, we performed a Parametric Empirical Bayes (PEB) analysis (Friston et al., 2003; Zeidman et al., 2019b) over the first-level DCM parameter estimates. PEB is a hierarchical Bayesian model that evaluates commonalities and differences among subjects in the effective connectivity domain at the group level. This method considers variability in individual connectivity strengths and reduces the influence of subjects with noisy data. Separate PEB analyses were conducted for each matrix (A: intrinsic connectivity, B: modulatory effects and C: effects of driving inputs) to prevent dilution of evidence by reducing the search space. After estimating the full model (with all connectivity of interest on) for each subject, the PEB approach performed Bayesian model reduction (BMR) and averaging (BMA) of the parameters across models weighted by the evidence of each model. Subsequently, as there is no concept of significance in Bayesian analysis, we have reported only parameters contributed to the model evidence with at least positive evidence, i.e. posterior probability (Pp) exceeding 0.73, that corresponds to positive (Pp: 0.73-0.95) , strong (Pp: 0.95-0.99) and very strong (Pp>0.99) evidence (Kass and Raftery, 1995).

Results

Fifty-five healthy participants underwent fMRI scans either in the morning or evening. These were distributed as 20 young adults scanned in the morning, 17 young adults in the evening, and 18 adolescents in the evening. During the scan, participants performed an auditory working memory task (n-back) under 4 different light conditions including low illuminance orange light, and three intensities of blue-enriched cool light. We examined how varying illuminance influenced the connectivity between three primary brain regions of interest involved in the task.

Univariate Analysis of the Response to 2-back vs. 0-back Task

Having controlled baseline brain activity using the 0-back task, we conducted a standard univariate analysis to isolate regions of interest that were responsive to the task, irrespective of light

condition (and of age group and time-of-day). A widespread set of regions showed activation in response to the task, consistent with previous literature (**Suppl. Table 9-11**). This analysis confirmed that the task was successful in triggering activation within the thalamus, commonly reported in the context of working memory (Dagenbach et al., 2001; de Bourbon-Teles et al., 2014), and in the prefrontal and parietal cortices which are typically involved in the verbal n-back task (Na et al., 2000; Owen et al., 2005; Wang et al., 2019). We selected our ROIs as the maximal activations within these areas. Specifically, we observed bilateral activation in the thalamus, the SMG and the IFJ, with a spatially broader activation in the left hemisphere (**Figure 6-2 A**), as well as in the anterior insula and cerebellum (**Suppl. Figure 9-5**). Thus, the first principal component of the BOLD time series was extracted from the left MDN, left SMG, and left IFJ, all engaged in the ongoing executive processes, to infer their respective neuronal activities. We then used DCM to examine the effective connectivity among these three regions under different light conditions in each group of subjects.

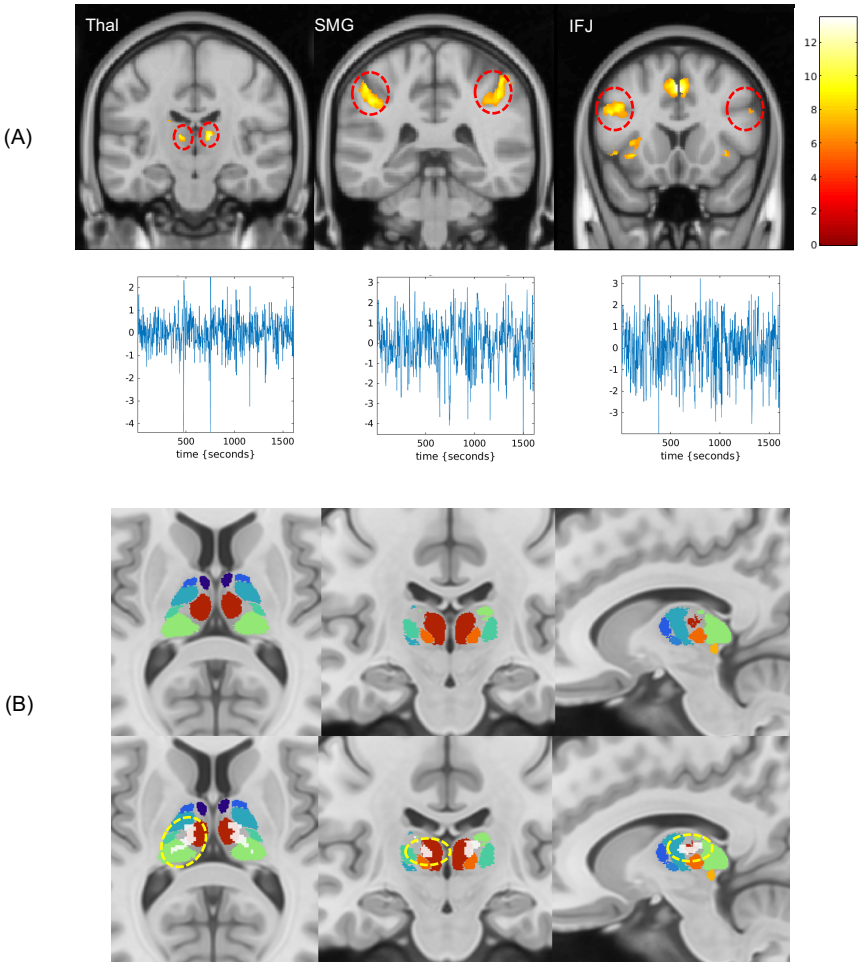


Figure 6-2: Activation and eigenvariate extracted from the 3 ROIs included in the DCM analysis.
A) Left: Bilateral thalamic activation in the mediodorsal nucleus (MDN), Middle: Bilateral parietal activation in the supramarginal gyrus (SMG), Right: Bilateral activation in the inferior frontal junction (IFJ). B) Top row: Thalamus parcellation map (Saranathan et al., 2021): MDN is shown in maroon. Bottom row: Thalamic activity (shown in white) overlaid on the parcellation.

Connectivity of the Reference Group - Adults Scanned in the Evening

To compare the modulatory impact of light on connectivity between morning and evening, as well as between adults and adolescents, we made a 3-group comparison. The adult group who underwent fMRI scans in the evening were considered as the reference for analyses, i.e. the group common to all comparisons that would provide the light induced modulation common to all 3 groups. The other two groups, which were adults scanned in the morning and adolescents scanned in the evening, were compared against this reference group to identify additive effects related to time-of-day (for adults) and age differences. DCM analysis in the reference group (**Figure 6-3 B**) showed that the 2-back task, a working memory challenge, compared to the 0-back task, predominantly activates the IFJ and SMG (Pp=1.0), indicating that these regions are primarily responsible for handling the cognitive demands of the task within our 3-region network. This means that interestingly, according to our analyses, the MDN did not receive direct task input within our network, suggesting that its role may be more about facilitating inter-regional communication rather than direct task-related processing. DCM also yielded very strong evidence (Pp=1.0) for self-inhibition in both the SMG and the MDN, suggesting intrinsic regulatory mechanisms that maintain stable activity levels. DCM further yielded very strong evidence for an excitatory connectivity from the MDN to both the SMG (Pp=1.0) and the IFJ (Pp=1.0), highlighting the MDN significant influence on SMG and IFJ activity. In addition, DCM provided very strong evidence for bilateral connectivity between the MDN and IFJ (Pp=1.0) that indicates a reciprocal relationship, where both regions influence each other with the MDN exerting excitatory effects while the IFJ provides inhibitory feedback. The last intrinsic connectivity with very strong evidence was the directed inhibitory connectivity from the IFJ to the SMG (Pp=1.0) that shows the IFJ's role in driving SMG activity. The overall pattern of excitatory thalamic inputs and inhibitory IFJ inputs supports complex task performance by balancing activation and regulation across these regions.

The primary objective of this study was to evaluate how light modulates connectivity. DCM analysis in the reference group (adults, evening), revealed positive evidence (Pp=0.74) for a strengthening impact of moderate illuminance (92 melEDI) on the connectivity from the SMG to the IFJ. This modulation suggests that under moderate blue-enriched light condition, the influence of the SMG on the IFJ is increased. Low illuminance orange light (0.16 melEDI) showed positive evidence (Pp=0.90) for a strengthening impact on the connectivity from the MDN to the SMG (**Figure 6-3 C**) This modulation suggests that in the evening, during the orange condition, the influence of the MDN on the SMG is increased.

This first analysis established the connectivity patterns in the reference group that were also present in the other 2 groups. We then assessed light-induced modulation that would come in addition to those shared effects, by contrasting the reference group to the morning adult group (adults) and the adolescent evening group to identify differences related to the time-of-day and age.

Modulation of Thalamus – Prefrontal Connectivity in the Morning

The DCM analysis comparing the impact of illuminance on connectivity showed positive evidence (Pp=0.79) that the highest-illuminance in the morning (190 melEDI) strengthened the connectivity from the MDN to the IFJ (**Figure 6-3 D**). The modulation of this thalamo-cortical connectivity suggests that, in addition to the light effects detected in the reference group, blue-enriched light has a time-dependent effect on brain connectivity and, in the context of executive functioning and in the morning, blue- enriched light may modulate neural processing and connectivity through this pathway, more effectively.

Modulation of Thalamus – Parietal Connectivity in Adolescents

The DCM analysis on the modulatory impact of light illuminance across different age groups indicated, with positive evidence (Pp=0.93), that moderate illuminance blue-enriched light strengthened the connectivity from the MDN to the SMG in adolescents (**Figure 6-3 E**). This modulation suggests developmental differences in the brain's responsiveness to light, with adolescents showing a strengthened influence of thalamus on SMG activity under the moderate illuminance, in addition to effect of low illuminance orange light detected in the reference group.

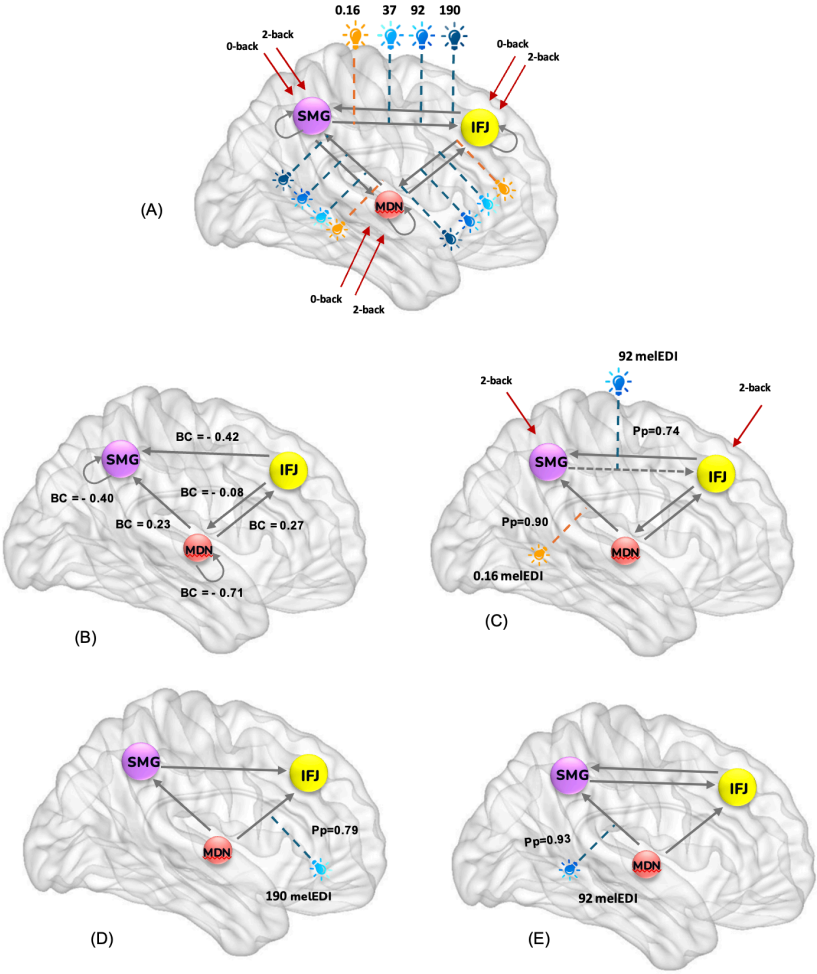


Figure 6-3: Effective connectivity results.

A) Initial model tested using the DCM framework. B) Baseline connectivity (Adults with fMRI in the evening). C) Modulatory impact of light in the reference group (Adults with fMRI in the evening) D) Differences between the connectivity parameters in the morning compared to the evening (in adults). E) Differences between the connectivity parameters in adolescents compared to adults (both in the evening). IFJ: inferior frontal junction: MDN: mediodorsal nucleus of thalamus; melEDI: melanopic equivalent daytime illuminance. Pp: posterior probability of the parameters. SMG: supramarginal gyrus.

Discussion

This study aimed to evaluate the impact of light illuminance on cognitive brain function and in particular on the crosstalk between brain regions during a cognitive challenge. We determined how changes in illuminance affect the connectivity within a brain network sustaining an ongoing auditory executive task composed of the MDN of the thalamus, the SMG in the parietal cortex, and the IFJ in the prefrontal cortex. We further explored how time-of-day, i.e. morning vs. evening, and age, with a focus on adolescents vs. young adults, could affect the light-induced modulation of connectivity. Firstly, we found that in young adults, moderate blue-enriched light strengthened the cortico-cortical connectivity from the SMG to IFJ in the evening. Unexpectedly, low illuminance orange light also exerted an impact on the thalamo-cortical connectivity from the MDN to SMG. These effects were also present in the morning young adult group and in the adolescent group, as they did not change with time-of-day or age. Secondly, blue-enriched light impacted the network differently in the morning with the most intense blue-enriched light affecting the thalamo-cortical connectivity from the MDN to the IFJ. Thirdly, adolescents showed a different response to light, with moderate-illuminance modifying the thalamo-cortical connectivity from the MDN to SMG. Overall, these results reinforce the view that the thalamus is key in mediating the acute impact of light on cognitive brain function and emphasize that the impact of light depends on the context of light administration. Our findings may have implications for the growing interest in developing lighting interventions aimed at optimizing cognition across ages.

Prior human fMRI research has repeatedly identified the thalamus as the subcortical brain area most consistently affected by light exposure during non-visual cognitive tasks (Vandewalle et al., 2007a, 2007b, 2006). With its diverse nuclei, the thalamus plays a crucial role in processing and forwarding sensory information to the cerebral cortex. It further integrates diverse types of inputs critical for cognitive function, including alertness signals, through the so-called thalamo-cortical loops. The pulvinar, which occupies a large part of the posterior part of the thalamus, has often been proposed as the thalamus nuclei mediating light impact and we recently provided support to this idea in the context of a morning light exposure and an auditory attentional task (Paparella et al., 2023). Focusing on executive functions in the context of an auditory n-back task, our current univariate analysis pointed towards the MDN, which is more medial than the pulvinar. Importantly, the thalamic ROI we focused upon in our prior publication on the impact of light on attention also encompassed smaller portions of several thalamus nuclei in addition to the pulvinar, including the MDN (Paparella et al., 2023). Likewise, the current thalamus ROI was focused on the MDN but

extended dorsally to include a small portion of the pulvinar. Both publications are therefore focusing on the same brain structures even if their pulvinar vs. MDN gradient is distinct. Similar to the pulvinar, the MDN is an association nuclei (not only relaying sensory information to the cortex) and it is important for executive functions such as attention, working memory and decision making (Mitchell, 2015; Mitchell and Chakraborty, 2013; Ouhaz et al., 2018). It is therefore in good position to convey the stimulating influence of light to the cortex.

Our univariate analysis further indicated that, similar to the attentional task, the SMG was strongly involved in the ongoing processes (the IPS reported in our prior publication consist of the sulcus continuing the gyrus of the SMG), as well as the IFJ, which is more specific to executive function. The connectivity between the thalamus and both of these cortical regions is of particular interest. The SMG plays an important role in working memory, particularly in verbal working memory tasks (Deschamps et al., 2014). As part of the parietal lobe, the SMG is involved in the phonological loop (Deschamps et al., 2014; Yue and Martin, 2022) and is essential for storing serial order information and manipulating verbal information and plays a key role in focusing and controlling attention. The thalamus to SMG connectivity, which we detect irrespective of light illuminance, may enhance the ability of the SMG to integrate sensory information and support phonological processing. The IFJ located within the frontal cortex is a key structure for cognitive control, particularly in tasks that demand executive functioning involving decision-making such as the n-back task (Sundermann and Pfleiderer, 2012). It helps with managing information, retrieval and update. The thalamus to IFJ connectivity change that we detect irrespective of light illuminance, can facilitate this process by modulating responses based on current cognitive demands and incoming sensory information and ensuring that decision-making and executive processes are informed by the latest sensory inputs.

When then considering the impact of illuminance on the 3-area-network, we first stress that we cannot determine which retinal photoreceptor mediates the connectivity changes we detected. While our rationale for conducting the study is based on ipRGCs maximal sensitivity to shorter wavelength, all conditions varied in terms of rod, cone and melanopsin stimulation. The light levels and spectra we administered it is likely that ipRGCs and cones contributed to our findings, with cones potentially contributing through their inputs to ipRGCs (Güler et al., 2008). While a classical response of rods is less likely, it cannot be ruled-out (Altimus et al., 2010).

The impact of moderate-illuminance we found in all participants on the cortico-cortical connectivity from SMG to IFJ (with moderate evidence; Pp=0.74) is in line with a previous study that has shown blue light exposure increases functional connectivity between the prefrontal cortex and multiple cortical regions, including the SMG (Killgore et al., 2022). It is likely to correspond to

a strengthening impact of top-down attentional processes mediated by the SMG on higher-order cognitive functions, potentially strengthening the integration of attentional process with executive functions. Additionally, the fact that only the moderate-illuminance blue- enriched light affected the SMG-IFJ connectivity may be due to a ceiling effect, where higher intensities do not yield additional effects or a response that follows an inverted U-shaped function. We further surprisingly found that the connectivity from the MDN to the SMG was influenced by low illuminance orange light, to which ipRGCs should be only weakly sensitive. This is likely to reflect a direct involvement of rods and/or cones that would trigger a visual response ultimately affecting the crosstalk between the MDN to SMG. Knowing that the MDN has been implicated in visual responses, our finding may reflect the influence of visual responses on alertness and attention, reminding that light effects always consist of a mixture of visual and NIF responses. Similar to the impact of blue-enriched light on the SMG-to-IFJ connectivity, the impact of orange light on the MDN-to-SMG connectivity could increase/optimize the attentional resources required for the ongoing cognitive processes.

Rod and cone signal could also reach the posterior thalamus and the SMG through the visual pathway with relays in the Lateral Geniculate Nucleus (LGN) and in the primary visual cortex. IpRGCs inputs could directly reach the thalamus through the paraventricular nucleus (Nascimento et al., 2008), the ventral LGN (the intergeniculate leaflet in rodents) (Muscat and Morin, 2006) or directly through the pulvinar (Maleki et al., 2012). IpRGCs signaling could also indirectly reach our networks through their dense projection to hypothalamus nuclei including the lateral hypothalamus (LH), as we recently suggested based on part of the same dataset (Campbell et al., 2024b) as well as through the locus coeruleus (LC) which received indirect inputs from the SCN, orchestrating circadian rhythmicity. Given the broad projections of the LH and LC and their involvement in alertness regulation, they could both influence MDN and SMG activity and connectivity. Determining which of these options is more likely will require further connectivity analyses including other brain regions such as the LC and LH.

Importantly, when focusing on time-of-day differences, we find that in the morning, the highest illuminance affects the MDN to IFJ connectivity. This could again correspond to the translation of the increase in alertness by light on frontal activity to improve the ongoing high-order executive processes. This is reminiscent of the impact of morning blue-enriched light on the thalamus/pulvinar connectivity to the parietal cortex (Paparella et al., 2023). The NIF impact of morning light may therefore primarily affect thalamocortical loops, to the parietal cortex in the case of attentional task and to both the parietal and frontal cortex in a more complex executive

task (Barber et al., 2020). This change in the crosstalk from thalamus to cortex would come on top of the parietal to prefrontal change in connectivity at least for executive processes as this connectivity was not tested for attentional processes – warranting further investigations. Since the highest illuminance did not affect the MDN to IFJ connectivity in the evening, our finding suggests that the dynamics of the impact of illuminance and its potential ceiling effect and/or inverted U-shape pattern varies across the day. The previous suggestion that light may be more beneficial in the morning than in the evening, when considering brain function from a regional activation perspective (Vandewalle et al., 2011b) may extend to connectivity which would be influenced by a broader range of illuminance in the morning. Light may be better able to improve alertness and/or attention when one has been awake and/or exposed to light for only a few hours compared to the end of the day.

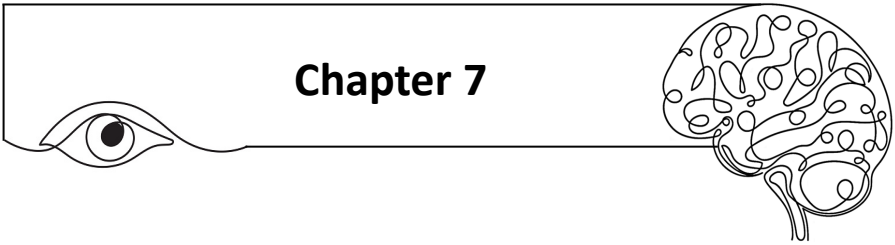
Critically also, when comparing age groups, we find that moderate illuminance increases the MDN-to-SMG connectivity in adolescents, compared to young adults. This suggests that in this age group blue-enriched light increases the thalamus impact on the attentional resources sustained by the SMG. This would come on top of the influence of orange light on the MDN-to-SMG connectivity (as well as the influence of moderate blue-enriched light on the SMG-to-IFJ connectivity). Adolescents may therefore be more affected by light than young adults in the evening particularly on a connectivity that may influence attention (Saalmann et al., 2012). This may be important given the current concerns regarding adolescents using LED screen devices, particularly in the evening (Touitou and Point, 2020). This further supports the development of specific light interventions in this age group to optimize evening alertness, attention and sleep in the evening, as investigated by others (Perrault et al., 2019; Schöllhorn et al., 2023). The age group difference we detect may, however, also arise from differences in maturation or wiring of the brain which is considered to be fully completed by age 25y (Talwar et al., 2023). The group difference could indeed be present at all times of day, i.e. also in the morning as it was not assessed in the present study. Future studies with more light conditions and comparing age groups at different times of day are needed to test the hypothesis we raised here. These studies should also include larger sample size, as despite our relatively large research effort to collect data in more than 50 individuals, the different age groups were still composed of 17 to 20 individuals, which may have hindered statistical power.

Finally, we refer to recent recommendations for the light level which should be used during the day (250 melEDI lux), in the evening (10 melEDI lux) and at night (darkness:1 melEDI lux) to enhance physiology, sleep quality, and wakefulness in healthy adults (Brown et al., 2022). The highest illuminance we administered was 190 melEDI and impacted brain connectivity in the morning

confirming that illuminance in relatively similar range to the recommendation affects brain functions. The moderate illuminance we administered was 92 melEDI lux and impacted connectivity in all groups (particularly in adolescents), confirming also that higher illuminance than recommended for the evening can affect brain functions.

Although the main focus of this study was on the modulation of brain connectivity by light, performance is an important factor to investigate, given the observed changes in connectivity. While performance data were not included in the current analysis, future investigations will explore how these connectivity changes relate to task performance, particularly in terms of cognitive functioning and the impact of light exposure. This will provide a more comprehensive understanding of the functional significance of light-induced connectivity modulation.

In summary, we show that light influences the information flow from the thalamus to cortical areas and between cortical regions, potentially reflecting how the impact of light on alertness and attention facilitates integration in a network highly relevant for executive functions. These effects are not detected in the entire network sustaining an ongoing cognitive process and are specific to the crosstalk between certain brain regions, with a potential central role of the posterior and dorsal thalamus (pulvinar and/or MDN). We further report that the time-of-day and brain development stage modulate the impact of light on brain functions. Overall, our findings add to the growing body of research building the promise of light interventions to optimize brain functions (and sleep) at different times of day and across the lifespan (Campbell et al., 2023).



Chapter 7

Cortical Excitability is Affected by Light Exposure: Distinct Effects in Adolescents and Young Adults

This chapter is based on our submitted paper:

Sharifpour, R., Balda, F., Paparella, I., Read, K., Leysens, Z., Letot, S., Campbell, I., Beckers, E., Collette, F., Phillips, C., Zubkov, M., Vandewalle, G. (2024) Cortical Excitability is Affected by Light Exposure: Distinct Effects in Adolescents and Young Adults.

Abstract

Light, particularly blue-wavelength light exerts a broad range of non-image forming (NIF) effects including the stimulation of cognition and alertness and the regulation of mood, sleep and circadian rhythms. However, its underlying brain mechanisms are not fully elucidated. Likewise, whether adolescents show a different NIF sensitivity to light compared to adults is not established. Here, we investigated whether cortical excitability, a fundamental aspect of brain function that depends on sleep- wake regulation, is affected by blue light and whether the effect is similar in young adults and adolescents. We used transcranial magnetic stimulation coupled to high-density electroencephalography (TMS–EEG) in healthy young adults (N=13, 24.2y ±3.4) and in adolescents (N=15, 16.9y±1.1). Our results showed that, in young adults, blue light affected cortical excitability following an apparent inverted-U relationship, while adolescents' cortical excitability was not significantly different under blue light compared to orange light. In addition, although light did not affect performance on a visuomotor vigilance task completed during the TMS-EEG recordings, cortical excitability was positively correlated to task performance in both age groups. This study provides valuable insights into the complex interplay between light, cortical excitability, and behavior. Our findings highlight the role of age in NIF effects of light, suggesting that brain responses to light differ during developmental periods.

Introduction

Besides enabling vision, light exerts a broad range of physiological, hormonal, and neurobehavioral effects that are not directly related to vision and are often referred to as non-image forming (NIF) effects of light (Campbell et al., 2023; Mahoney and Schmidt, 2024). NIF effects are primarily mediated by a subclass of retinal ganglion cells (RGCs) that act as photoreceptors by expressing the photopigment melanopsin (Campbell et al., 2023; Mahoney and Schmidt, 2024). These intrinsically photosensitive RGCs (ipRGCs) combine rods and cones outputs to their own response to light and funnel light signal to many (subcortical) parts of the brain involved in the regulation of the circadian system, sleep need, mood and cognition (Alkozei et al., 2016b; Altimus et al., 2008; LeGates et al., 2012; Zhang et al., 2021). Since melanopsin is maximally sensitive to short wavelength blue light, at around 480 nm, NIF impacts of light on brain functions are mostly driven by the blue-wavelength content of light (Campbell et al., 2023; Mahoney and Schmidt, 2024). A basic aspect of the brain functioning is cortical excitability that can be defined as the responsiveness and response selectivity of cortical neurons (Rosanova et al., 2011). It is therefore

fundamental to cognitive brain functions and dictates the impact of an incoming stimulus on cortical activity and on behavior. Cortical excitability depends on prior sleep-wake history and circadian phase (Gaggioni et al., 2019; Huber et al., 2013; Ly et al., 2016). It remains relatively stable during the day while well rested and sharply increases if one stays awake (Huber et al., 2013) such that overnight increase of cortical excitability is correlated to performance decrement (Ly et al., 2016) and is therefore likely to contribute to the detrimental effect of sleep loss on cognition. The relationship between performance and cortical excitability may follow an inverted U-shape function where an optimal mid-range level of excitability, likely happening during the day when well-rested (Valdez et al., 2012), is associated with optimal performance while lower or higher levels lead to poor cognitive outcomes. Cortical excitability depends on several environmental factors that directly or indirectly affect alertness or sleepiness level, including alcohol and potentially caffeine consumption (Kaarre et al., 2018; Naim-Feil et al., 2016; Zulkifly et al., 2021). It is therefore plausible that ambient light could also affect cortical excitability. Findings of a small-scale study, carried out close to 3 decades ago on seven young adults (21-25y), suggested in fact, that there might be an inverted U-shape relationship between light-induced increase in arousal and an indirect measure of cortical excitability inferred from an evoked EEG response (Higuchi et al., 1997). Besides this early report, whether exposure to light affects cortical excitability is not established.

Adolescence may be of particular interest when focusing on NIF effects of light. Optimizing the lighting in classrooms has indeed been proposed as a promising simple means to improve alertness and performance at school (Keis et al., 2014; Sleegers et al., 2013). Research also reported that NIF effects depend on the prior light history, such that prior exposure to high light levels over the preceding hours, days or even weeks, may reduce NIF effects (Chang et al., 2006; Hébert et al., 2002). Adolescents are high consumers of LED devices, typically enriched in blue light, and may spend more time outdoors, they may therefore present a reduction in NIF effects of light on brain function. Adolescents, however, are characterized by a late chronotype (i.e. intrinsic time- of-day preference to be physically and/or mentally active), and late chronotypes in adults are typically associated with a higher sensitivity to NIF impact of light (Wright et al., 2013) that can lead to an increase in NIF effects.

Although it is established that exposure to light affects cognitive brain function (Campbell et al., 2023), whether spectral composition of light impacts cortical excitability, and whether it happens differently in adolescents versus young adults, is not yet established. Such questions need to be

resolved before one can use the flexibility of LEDs to design truly individualized human-centered lighting.

In the present study, we used transcranial magnetic stimulation coupled with high-density electroencephalography (TMS-EEG), as a non-invasive tool to assess cortical excitability in vivo in 13 healthy young adults aged 19-30y while they were exposed to light of different illuminance levels (as computed in Melanopic Equivalent Daylight Illuminance - melEDI lux). We further assessed whether cortical excitability was correlated to the performance on a concomitant visuomotor vigilance task. Data were also collected in 15 healthy adolescents aged 15-18y to determine whether sensitivity to the impact of light on cortical excitability was altered in this age group. We hypothesized that in young adults, cortical excitability would increase by increasing melanopic illuminance and performance on the task would be correlated with cortical excitability. We further anticipated that the impact of light would be different in adolescents with no prior expectation on the directionality of the difference.

Method

The protocol was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. Participants provided their written informed consent and received financial compensation.

Participants

Between March-2022 and September-2023, thirty-six healthy volunteers participated in the study, 19 adolescents (16.8±1.0 years old, 6 Females) and 17 young adults (24.9±3.9 years old, 9 Females). Exclusion criteria were as follows: BMI>28; recent psychiatric history; severe trauma; sleep disorders; addiction; chronic medication; smoking, excessive alcohol (>14 units/week) or caffeine (>4 cups/day) consumption; night shift work during the last year; transmeridian travel during the past 2 months; anxiety (Morin et al., 1999) or depression (Beck et al., 1988); poor-sleep quality (Buysse et al., 1989); excessive self-reported daytime sleepiness (Johns, 1993); and pregnancy. Seven participants were excluded from the analyses due to poor data quality (i.e. TMS artefact masking the response of interest) and one participant was excluded due to both cortical excitability metrics > 3 standard deviations (SD) compared to the rest of the sample (outlier). Thus, the data presented here includes twenty-eight participants (15 adolescents and 13 young adults). **Table 7-1** summarizes the demographic characteristics of the final sample.

Table 7-1: Demographic characteristics of the participants included in the analyses.

	Adolescents	Adults	Comparison (t-test)
Number of Subjects	15	13	
Age (y)	16.9±1.1	24.2±3.4	
Sex: Female (Male)	4 (11)	5 (8)	P=0.52
Body mass index (kg/m^2)	21.8±2.4	22.4±2.3	P=0.45
Caffeinated drinks(cup/day)	0.4±0.7	1.1±0.9	**P=0.03**
Alcohol (unit/week)	2.4±4.3	2.2±2.0	P=0.86
Depression (BDI-II[a])	7.4±4.7	5.1±3.0	P=0.36
Anxiety Level (BAI[b])	6.5±6.0	5.9±3.0	P=0.77
Chronotype (HO[c])	42.5±8.3	42.6±8.0	P=0.98
Sleep time (night before the TMS session)	23:08±0:41	23:12±0:46	P=0.65
Wake time (day of the experiment)	7:08±0:50	7:46±1:09	P=0.19
Sleep duration (h) (night before the TMS session)	7.6±1.2	8.3±1.2	P=0.13
Sleep Quality (PSQI[d])	4.3±1.5	4.7±1.6	P=0.83
Habitual daytime Sleepiness (ESS[e])	5.9±3.9	6.9±2.8	P=0.45
Season of experiment *	-0.2±0.6	-0.2±7	P=0.90
Seasonality (SPAQ[f])	1.1±1.0	1.2±0.8	P=0.83
Eye color: Bright (Dark) **	11 (4)	7 (6)	P=0.30
Electrical Field (Mean±SD)	115.0±16.7	109.3±10.4	P=0.08
Distance (Mean±SD) ***	33.0±8.5	32.1± 8.9	P=0.67

[a]. Beck's Depression Inventory II
[b]. Beck's Anxiety Inventory
[c]. Horne and Östberg Questionnaire
[d]. Pittsburg Sleep Quality Index
[e]. EPWORTH Sleepiness Scale
[f]. Seasonal Pattern Assessment Questionnaire
* All participants were right-handed.

Experimental Protocol

To avoid excessive sleep restriction while maintaining real-life conditions, participants were asked to keep a regular sleep–wake schedule (±1h), in agreement with their preferred bed and wake-up times, for five days preceding the in-lab experiment. Compliance was verified using sleep diaries and wrist actigraphy (Actiwatch,Cambridge Neurotechnology,UK). Additional methodological information can be found as supplementary method (**Appendix 6**).

On the experimental day, participants arrived at the laboratory between 13:00-14:00. To control for recent light history, participants were maintained in dim light (<10 lux) for 1:28±0:27, during which the optimal TMS parameters (i.e., location, intensity, coil orientation) providing artifact free TMS- EEG recordings were determined and set. The stimulation target was set to the superior frontal gyrus (SFG) on the dominant hemisphere (left hemisphere as all our participants were right-handed). This brain area was chosen for the following reasons: (1) the SFG is highly sensitive to sleep pressure, including at the neuronal level, just like the entire frontal lobe (Cajochen et al., 2002); (2) it plays an important role in cognitive performance (Boisgueheneuc et al., 2006); and (3) its stimulation does not cause muscle activation, which is a source of EEG signal contamination.

Light Set-up and Protocol

The light source used in this study was a tunable 35cm×45cm light LED box (EOS,Balder,Huy,Belgium) which allowed us to create three light conditions including orange light served as control light condition, and active lower-intensity and higher-intensity blue light conditions. The illuminance level of each light condition was adjusted manually for each participant such that the orange light and lower-intensity blue light conditions had the same photopic illuminance of 30 lux at the eye level while the photopic illuminance for the higher-intensity blue light condition was increased to 60 lux (**Suppl. Table 9-12**). **Figure 7-1** shows the spectrums of the three light conditions.

Each light session began with 1-2 minutes of light adjustment followed by a two-minute eye-open waking (rest) EEG recording. In each Light session, TMS-EEG recording pre-exposure time was approximately 5-minutes, and the entire TMS-EEG recording time was ~10 minutes. The order of the orange and lower-intensity blue sessions was randomized, with the higher-intensity blue session always being last. The main question of this study was to determine the impact of blue light on cortical excitability compared to the orange light with the same photopic illuminance. Therefore, given the long duration of the entire protocol (around 5 hours) and the possibility of

teenage volunteers becoming fatigued and withdrawing early, before the last session of the experiment (happened for one subject), the order of the sessions was decided as explained so that we would anyway have the two sessions needed to answer our main research question. The three sessions were separated by at least a 15-minute washout period in dim light (<10 lux).

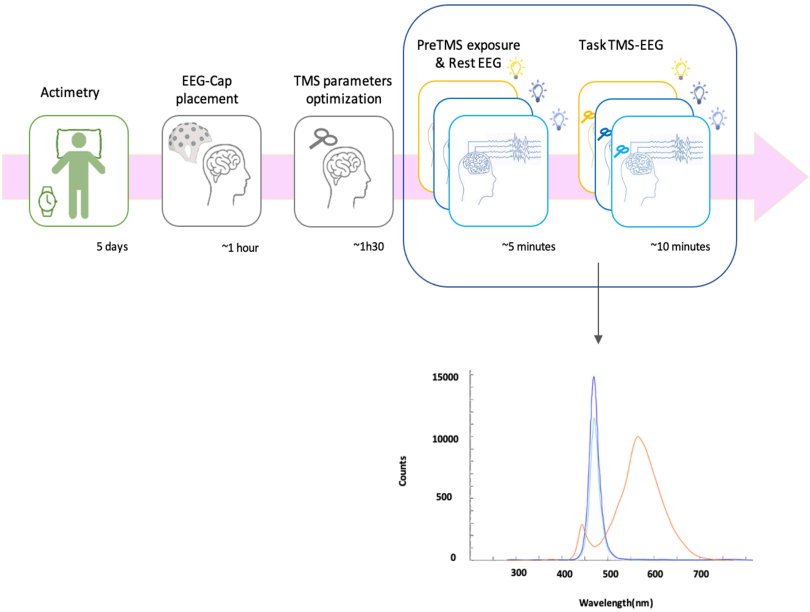


Figure 7-1: Graphical representation of the TMS protocol and the spectrums of light conditions. *Polychromatic orange light at 24 melEDI lux; Monochromatic lower-intensity blue light at 312 melEDI lux, and monochromatic higher-intensity blue light at 625 melEDI lux.*

TMS-EEG Acquisition

A Focal Bipulse 8-shape coil (Eximia; Nexstim, Helsinki, Finland) was used to generate TMS pulses. Stimulation target was located on individual structural MRI using a neuronavigation system (Navigated Brain Stimulation; Nexstim, Helsinki, Finland), which allows for exact target localization and reproducible evoked EEG responses (FDA presurgery approval) (Rosanova et al., 2011). The neuronavigation system ensured that hotspot location remained constant across sessions within an individual (±2mm). The EEG cap was worn by participants throughout the entire protocol, and electrode impedance was kept below 5 kΩ. The signal was bandpass filtered between 0.1 and 500

Hz and sampled at 1450 Hz. The protocol ended with a neuronavigated digitization of each electrode's location. TMS-induced auditory EEG potentials (AEP) and bone conductance were minimized by playing a continuous loud pink masking noise through earplugs and putting a thin foam layer between the EEG cap and the TMS coil, respectively (Daskalakis et al., 2012). Following the last session, 30-40 stimulations were delivered parallel to the scalp in a sham session while the noise was playing at the same level. This session confirmed absence of AEP in all subjects.

Each session included around 250 TMS stimulations. The interstimulus interval varied randomly from 1900 to 2200 ms. The coil recharging time was set at 900 ms after TMS. TMS-evoked potentials (TEPs) were recorded using a 60-channel TMS-compatible EEG amplifier (Eximia; Nexstim, Helsinki, Finland). The reference and ground electrodes were placed on the forehead. Two extra bipolar electrodes were also used to record the electrooculogram (EOG).

Wake EEG Acquisition

Prior to each TMS session, eye-open rest-waking EEG was recorded using the same 60-channel TMS-compatible EEG (+2 EOGs) amplifier. Participants were asked to fixate on a black dot, placed on the light box in front of them, for 2 minutes while relaxing and avoiding excessive blinking.

Visuospatial Vigilance Task

Participants were instructed to perform a compensatory tracking task (CTT) (Makeig and Jolley, 1995) during the TMS-EEG recordings. Using a trackball device, the aim was to maintain a constantly moving, randomly positioned cursor on a fixed target in the center of a black background on a computer screen that was set to the lowest brightness. This task was preferred to psychomotor vigilance task (PVT) during TMS-EEG recordings because it simply requires constant, smooth and limited movement of a single finger and allows for continuous vigilance monitoring (Cardone et al., 2021) . In this task, a lapse was defined as a time during which the cursor remained outside a 200 by 200 pixels box centered on the target for more than 500 ms following the last trackball movement. Task performance was calculated as the average distance between the target and moving cursor after excluding lapse periods.

TMS-EEG Analysis

TMS-EEG data preprocessing was performed using MNE python package (Gramfort, 2013) (https://mne.tools/stable/index.html). Continuous EEG recordings were first high-pass and low-pass filtered using an IIR 4th order Butterworth with a cut-off frequency of 1 Hz, and an IIR 15th

order Butterworth with a cut-off frequency of 70 Hz, respectively. To minimize the DC offset of the signal, an IIR 4th order Butterworth band-stop filter with a 48-52 Hz range, was applied. Filtered data was first visually inspected to identify and remove bad channels (flat-line or highly noisy/artifactual channels). Individual trials were then split in epochs between -800 to 800 ms post-TMS and bad epochs were rejected during the second run of visual inspection. The remaining epochs were then re-referred to the average of all good channels. Independent components of the preprocessed EEG recordings were computed using the fastICA algorithm (Hyvarinen, 1999) in order to remove clear TMS-induced artifacts. Independent components were then visually inspected using power spectral density, spatial distribution, and variance distribution over epochs. To minimize data modification, only components representing clear TMS-induced artifacts were set to zero, and the remaining components were used to reconstruct the EEG signals. Artifact free trial epochs were epoched one more time, this time to a shorter period i.e., -300 to 300 ms post TMS. EEG recordings were again successively re-referenced to the average of all good channels and baseline corrected using a window from -101 to -1.5 ms pre-TMS. Epochs were then averaged to have the mean evoked response of each channel in each session.

Cortical excitability was inferred from the amplitude and slope of the first EEG component (0–35 ms) of the TEP measured at the artifact-free electrode closest to the hotspot (i.e. the location with highest TMS-induced electrical field estimated by the neuronavigation system). The latter electrode was always located in the stimulated brain hemisphere. It could vary across participants but remained constant at individual level.

Wake EEG Analysis

Waking EEG data were analyzed using MATLAB (2019b, The Mathworks Inc,Natick,MA). Data pre-processing was performed using Statistical Parametric Mapping 12 (SPM12, http://www.fil.ion.ucl.ac.uk/spm). Artifacted channels were rejected after visual inspection. Continuous EEG recordings were re-referenced to the average of all good electrodes and downsampled from 1450 to 500 Hz. Data were then manually and visually scored offline for artifacts (eye blinks, body movements, and slow eye movements).

Power spectral densities were computed using a fast Fourier transform on artifact-free 4s windows, overlapping by 2s, using the Welch's method (pwelch function in MATLAB).

EEG activity was computed over frontal region (F3, F1, Fz, F2, F4, FC5, FC3, FC1, FCz, FC2, FC4, FC6) for theta (4.25–8 Hz) and alpha (8.25-12 Hz) frequency bands over the entire 2-minute recording.

Statistical Analysis

All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). Generalized linear mixed models (GLMM; PROC GLIMMIX SAS procedure) were applied separately in each age group on TEP amplitude, TEP slope, power spectra and task performance as dependent variables according to their distribution estimated using the allfitdis function in MATLAB (developed by Mike Sheppard, part of the MvCAT package), with subject (intercept and slope) effect included as a random factor, light conditions (3 illuminance levels) as repeated measures with autoregressive correlation type 1 (ar(1)) and session-order, sex , age, and BMI as covariates. Direct *post hoc* tests of the main analyses were corrected for multiple comparisons using a Tukey adjustment. In each age group, additional models included the following potential confound variables separately: chronotype, seasonality, depression and anxiety indices, eye color, season, sleep duration (prior night), daytime sleepiness, sleep quality, insomnia index, subjective sleepiness before and after each session, average habitual caffein and alcohol consumption, electrode of interest distance from hotspot or alpha/theta power. For simplicity' sake, GLMMs were first performed on each age group separately and then in another GLMM, age group and illuminance-by-age group interaction terms were included to seek statistical differences between the groups.

Results

Cortical Excitability Increases Under Moderate Blue Light Exposure and Is Correlated to Performance on the Vigilance Task in Young Adults

We extracted cortical excitability metrics as both the amplitude and slope of the earliest EEG response evoked by the TMS pulses (TEP; 0–35ms post-TMS) (Huber et al., 2013), measured at the electrode closest to the hotspot. Statistical analyses employing both metrics separately as dependent variable revealed a significant main effect of the light condition ($p<0.02$), and no main effect of the other covariates (**Table 7-2**). *Post hoc* contrasts showed that compared to the orange light (24 melEDI lux) , both the amplitude and the slope of the TEP were increased during the lower-intensity (312 melEDI lux) blue light exposure (amplitude: $t=-3.05$, $p=0.005$; slope: $t=-2.58$, $p=0.016$) but not during the higher-intensity (624 melEDI lux) blue light (amplitude: $t=-1.11$, $p=0.27$; slope: $t=-1.00$, $p=0.33$). TEP amplitude during the later 624 melEDI lux blue light exposure

showed a statistical trend (t=1.94, p=0.06) to be lower compared to 312 melEDI lux blue light, while no difference was detected when comparing TEP slope (t=1.58, p=0.13) (**Figure 7-2 A**).

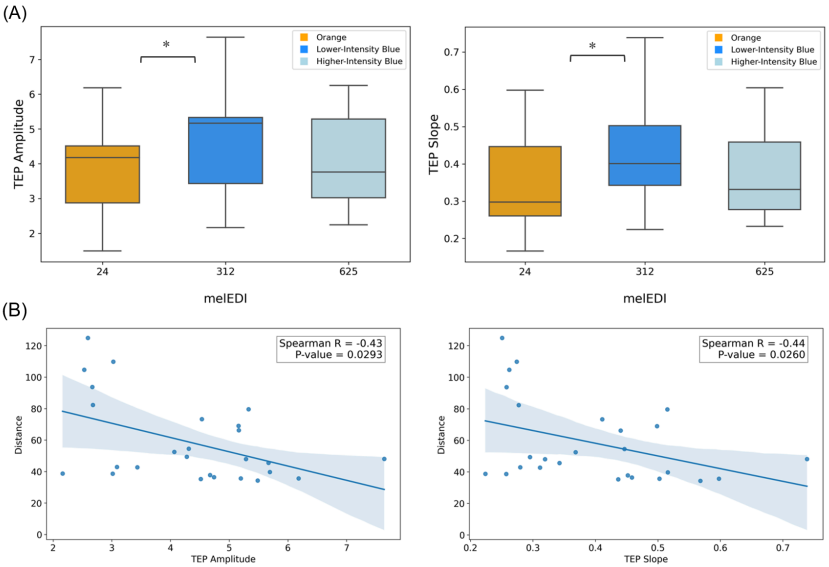


Figure 7-2 : Cortical excitability results in young adults.
TEP amplitude and slope under different light conditions (A). Regression plots of the association between TEP amplitude and slope with performance on the visuomotor task (B). Spearman R is indicative and do not substitute for GLMM outputs.

Including one of the following potential confounding factors in separate models did not alter the findings: chronotype, seasonality, depression and anxiety indices, eye color, season (in which the sessions were performed), sleep duration (prior night), daytime sleepiness, sleep quality, insomnia index, subjective sleepiness before and after each session and average habitual caffein and alcohol consumption.

Each TMS-EEG recording was initiated after 5-minute of light exposure and lasted about 11 minutes (11.5±1.2 minutes). They were preceded by a 2-minute recording of the spontaneous EEG activity while quietly awake (1-to-3 minutes post-light onset). We computed the power of the EEG over the theta (4.25-8Hz) and alpha (8.25-12Hz) bands as markers of sleepiness/sleep need and alertness, respectively (Cajochen, Foy and Dijk, 1999; Xavier, Su Ting and Fauzan, 2020). Statistical analyses yielded no significant variation in theta or alpha power across the light conditions (**Table**

7-2) indicating that baseline brain activity did not differ between the light conditions. Importantly, including theta and alpha power as covariates in our main GLMM did not modify our main statistical outputs.

Table 7-2: Statistical outcomes of GLMMs with the cortical excitability metrics and theta/alpha spectral power versus the light melEDI and covariates.

Adults

	Light Condition	Session	Age	Sex	BMI
TEP Amplitude	F(1,23)=8.73 **P = 0.007** **R^2 = 0.27**	F(1,23)=0.46 P = 0.50	F(1,9)=0.50 P = 0.50	F(1,9)=0.05 P = 0.83	F(1,9)=0.05 P = 0.82
TEP Slope	F(1,23)=6.37 **P = 0.019** **R^2 = 0.22**	F(1,23)=0.00 P = 0.98	F(1,9)=0.80 P = 0.39	F(1,9)=0.22 P = 0.65	F(1,9)=0.01 P = 0.93
Theta Power	F(1,23)=0.04 P = 0.82	F(1,23)=0.46 P = 0.50	F(1,9)=0.97 P = 0.35	F(1,9)=1.86 P = 0.20	F(1,9)=1.07 P = 0.33
Alpha Power	F(1,23)=2.96 P = 0.10	F(1,23)=2.82 P = 0.11	F(1,9)=0.52 P = 0.49	F(1,9)=0.16 P = 0.70	F(1,9)=0.55 P = 0.48

Adolescents

	Light Condition	Session	Age	Sex	BMI
TEP Amplitude	F(1,26)=0.09 P = 0.76	F(1,26)=0.02 P = 0.90	F(1,11)=1.12 P = 0.31	F(1,11)=0.01 P = 0.93	F(1,11)=9.36 **P = 0.01** **R^2 = 0.46**
TEP Slope	F(1,26)=0.01 P = 0.92	F(1,26)=0.05 P = 0.82	F(1,11)=1.44 P = 0.25	F(1,11)=0.11 P = 0.75	F(1,11)=6.23 **P = 0.03** **R^2 = 0.36**
Theta Power	F(1,26)=0.07 P = 0.79	F(1,26)=0.17 P = 0.68	F(1,11)=1.13 P = 0.31	F(1,11)=0.16 P = 0.70	F(1,11)=0.08 P = 0.78
Alpha Power	F(1,26)=3.01 P = 0.094	F(1,26)=0.67 P = 0.42	F(1,11)=3.12 P = 0.10	F(1,11)=0.04 P = 0.85	F(1,11)=1.28 P = 0.28

In the next step we considered the performance on the visuomotor vigilance task completed during the TMS-EEG recording. All participants performed the task well as indicated by the low number of lapses (1.92±3.1). Statistics indicated that performance was not significantly affected by the light condition ($p>0.1$) and yet it was significantly correlated to both the amplitude ($R=-0.43$, $p<0.03$) and the slope ($R=-0.44$, $p<0.03$) of the TEP (**Figure 7-2 B**), such that higher cortical excitability was associated with better performance (shorter distance between the moving and fixed dots).

No Changes in Cortical Excitability Under Different Light Conditions in Adolescents

In adolescents, statistical analyses, using TEP amplitude or slope as dependent variable, did not reveal a significant main effect of light condition ($p>0.7$) (**Figure 7-3 A; Table 7-2**), nor other covariates (except BMI, $p=0.03$). Including the same potential confounding factors in separate models as in adults did not change the statistical outputs. Likewise, theta and alpha immediately prior to the TMS session did not change across the light conditions ($p>0.09$; **Table 7-2**). Again, similarly to adults, including theta or alpha power in the model seeking for an impact of the light condition on the cortical excitability metrics did not modify the statistical outputs of the models (**Table 7-2**). Examining performance on the visuomotor vigilance task, the statistics revealed similar findings to those found in young adults. Still similarly to adults, performance on the visuomotor was not significantly affected by light condition ($p>0.2$), but it showed significant correlation with both the amplitude ($R=-0.57$, $p=0.0004$) and the slope ($R=-0.50$, $p<0.0028$) of the TEPs (**Figure 7-3 B**).

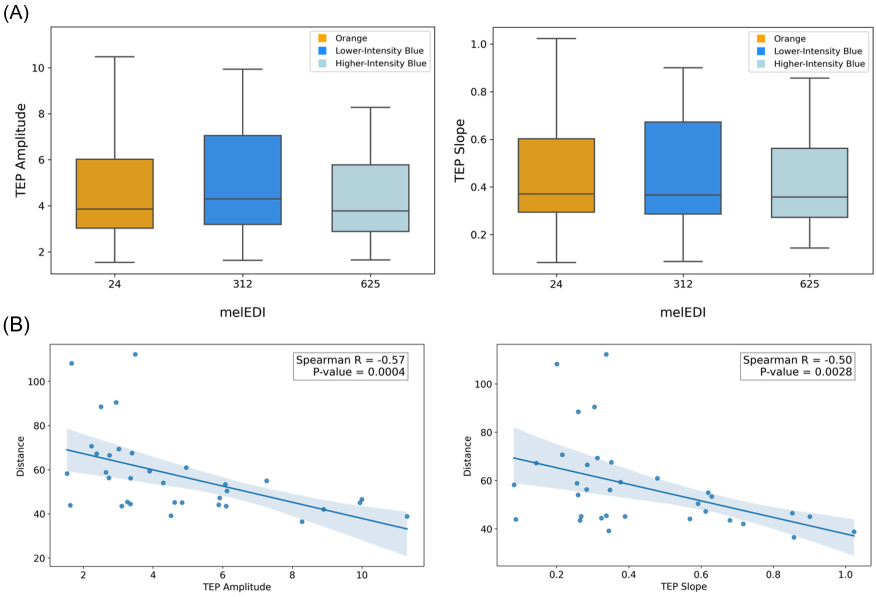


Figure 7-3: Cortical excitability results in adolescents.
TEP amplitude and slope under different light conditions (A). Regression plots of the association between TEP amplitude and slope with performance on the visuomotor task (B). Spearman R is indicative and do not substitute for GLMM outputs.

In our final set of analyses, we made a direct group comparison to seek for light condition-by-age group interaction controlling for the same covariates. The GLMM including TEP amplitude as dependent variable yielded a statistical trend for both light condition ($F(1,50)=3.81$; $p=0.056$) and light condition-by-age group interaction ($F(2,50)=2.77$; $p=0.072$). Conversely, the GLMM including TEP slope as dependent variable revealed no effect of light condition ($F(1,50)=2.77$; $p=0.10$) or light condition-by-age group interaction ($F(2,50)=1.68$; $p=0.20$).

Discussion

We used TMS–EEG to test whether illuminance affected cortical excitability. We showed that, in healthy young adults, the amplitude and slope of TMS evoked potential increased from lower (~24 melEDI lux) to moderate (~312 melEDI lux) melanopic illuminance, while they may decrease if

melanopic illuminance is further increased (~625 melEDI lux). Despite the limited age gap between our two age groups, these effects of light were not detected in adolescents, in which TEPs did not significantly change by light condition. Intriguingly, in both age groups, performance on a visuomotor vigilance task was not affected by the light condition and was yet significantly positively related to the amplitude and slope of TEPs. Our findings add to the previously reported multiple NIF effects of light on physiology and behavior and show that cortical excitability, which is a basic and fundamental aspect of brain function, depends on environmental light. Our results also suggest that the sensitivity to NIF impact of light on cortical excitability changes from adolescence to young adulthood. Our findings further suggest that optimal cortical excitability changes over different timescales. The increase in cortical excitability we detected in young adults between the orange and lower-illuminance blue light can only be attributed to the higher content in blue-wavelength photons of the latter light. Both light conditions were indeed equal in terms of photopic illuminance (in lux) while they differed markedly in NIF (melanopic) illuminance as indexed by the melEDI. This strongly suggests that ipRGCs contribute to the increase in cortical excitability we detected. Their projections to many subcortical structures involved in the regulation of alertness (and sleep), including the hypothalamus, may mediate this impact. These subcortical structures would then pass on light stimulating impact to the cortex, either directly, or indirectly through the locus coeruleus in the brainstem (Gaggioni et al., 2014) or through the pulvinar in the thalamus (Paparella et al., 2023; Vandewalle et al., 2009a) or a combination of multiple subcortical structures. We are, however, in no position to ascertain that only ipRGCs are involved in the effects we detected and stress that other retinal photoreceptors are most likely mediating at least part of the impact of light on cortical excitability, potentially through their inputs to ipRGCs (Güler et al., 2008).

Our findings in young adults are further compatible with an inverted U-shape relationship between melanopic illuminance and cortical excitability, where increasing illuminance would initially increase cortical excitability before inducing a decrease if illuminance is further increased (though as statistical trends only). This is in line with an early indirect suggestion based on EEG-evoked potential collected in a small sample, relating the impact of light to an effect on the alpha power of the quietly resting EEG (Higuchi et al., 1997). This suggested that arousal change would underlie the inverted U-shape relationship between light illuminance and cortical excitability, such that an optimal range of arousal would be associated with an optimal range of excitability. We did not observe an impact of illuminance on alpha or theta EEG power and cannot therefore directly relate our findings to changes in alertness or sleepiness. This may be because quiet resting brain activity

was recorded after only 1-minute of exposure to light which may have been short to induce detectable changes. The impact of light on alertness during the day has in fact not been consistently reported (Dumont and Carrier, 1997; Lok et al., 2018; Segal et al., 2016; Smolders et al., 2018) and may depend on the study protocol, light quality and the employed technique (Mu et al., 2022; Siraji et al., 2022).

To guarantee that at least 2 TMS-EEG sessions were completed by all participants, which allowed for testing our main research question (i.e. does illuminance affect cortical excitability?), the TMS-EEG session with brighter blue light exposure was always performed last. This limitation of the protocol was partly addressed by including session order in our statistical models. We cannot exclude, however, that the trend for a decrease in cortical excitability we observed under higher melanopic illuminance is not in part due to a change in time-of-day. Cortical excitability was indeed reported to decrease in the evening hours, 2-4 hours later than our protocol (Ly et al., 2016). Likewise, although we do not have any indication of this, the brighter blue light exposure might also have triggered more visual discomfort and contributed thereby to the decrease in cortical excitability. Replication of our findings in a larger sample size and a proper session randomization is therefore warranted to definitely establish an inverted U-shape relationship between melanopic illuminance and cortical excitability.

Contrary to our expectation, in adolescents, cortical excitability was not significantly changed by illuminance. This could be attributed to either higher or lower sensitivity to light. The theoretical greater transparency of crystalline lens and larger pupil size of adolescents might make them more sensitive to light (Eto et al., 2021, 2020; Najjar et al., 2016) such that a ceiling effect would already be induced by the orange light. However, we did not characterize the crystalline or pupil of our participants. Adolescents are also more prone to be later chronotypes when late chronotype has been suggested to increase the sensitivity to NIF impacts of light. Chronotype is however unlikely to have significantly contributed to our findings as it did not significantly differ between young adults and adolescents in our sample. On the other hand, adolescents may be less sensitive to light such that none of the light conditions we administered affected cortical excitability. Adolescents were likely exposed to more outdoor and/or artificial light over the hours or days preceding the experiment. Despite the standardization of the recent history implemented in the protocol (over the 2h30 preceding the first light exposure), this difference in light history may have reduced their sensitivity to light (Chang et al., 2011; Hébert et al., 2002). However, given the recommendation for effective light exposure during the day (melanopic lux > 250 melEDI) and the fact that both blue light conditions exceeded this threshold—especially high-intensity blue at 625 melEDI—it seems

unlikely that cortical excitability remained unchanged under blue light or reached a ceiling with orange light. We speculate that light may indeed influence cortical excitability under both blue conditions, but due to adolescents' heightened sensitivity to light, cortical excitability may have fallen at the lower end of the inverted U-shaped function. This could result in no observable differences between the blue light conditions and orange light, as well as between lower-intensity and higher-intensity blue light condition. The inclusion of session recorded in dim light or in darkness could help determining whether the light exposure we administered induced a significant change in cortical excitability or not.

Still contrary to our expectation, we did not observe a significant impact of melanopic illuminance on performance. Similar to alertness, a significant impact of light on behavior during the day is not always reported and may depend on the exact procedures of the protocols (Lok et al., 2018; Phipps-Nelson et al., 2003; Segal et al., 2016). The difficulty of the visuomotor task we administered was undoubtedly low such that individual performance might have been ceiling across the light conditions. This explanation appears however unlikely to fully explain the absence of light effect on performance since we did find a positive correlation between cortical excitability with vigilance task performance. Performance varied, irrespective of the light condition, in proportion of the variation in cortical excitability. While previous studies reported that the increase in cortical excitability induced by overnight sleep deprivation is associated with poorer performance following a putative inverted U-shape (Ly et al., 2016), our findings indicate that under well-rested condition in the afternoon, higher cortical excitability is related to better performance. There may be therefore distinct association between cortical excitability and behavior over different timescales. Sleep deprivation may increase cortical excitability far beyond its optimum level and result in poor performance, while increase in cortical excitability toward an optimum level at a given moment of the normal and well-rested waking day results in improved behavior. These relationships would be equally present in adolescents and young adults. In a smaller time scale, at a given moment of the normal waking day, light exposure, a common environmental factor, can also modulate cortical excitability following an inverted U-shape in young adults and thereby putatively affect behavior, though we provide no evidence in support of this later hypothesis. In adolescents, the impact of light on cortical excitability would be distinct and follows a pattern that remains to be established. This is because of the different sensitivity to light either due to difference in their developing physiology or in light exposure habits. These putative views are summarized in **Figure 7-4**.

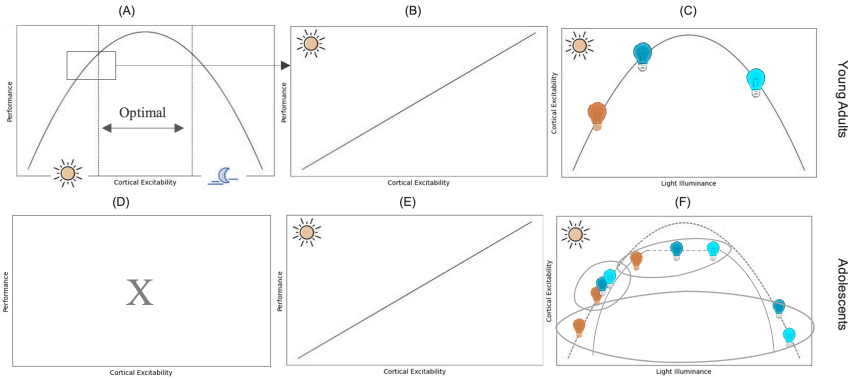
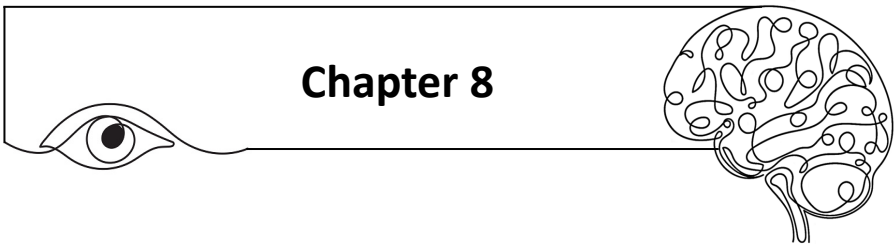


Figure 7-4: Putative schematic representation of the relationships between cortical excitability, performance and light illuminance.
(A) In adults, cortical excitability increases with time awake, and correspondence change in performance follows an inverted-U shaped function. Under well-rested condition (current study) higher cortical excitability leads to better performance (B) whereas under extended wakefulness condition, higher cortical excitability has detrimental effects on performance. Our findings suggest an inverted U-shaped relationship between illuminance and cortical excitability in adults (C). The relationship between cortical excitability and performance is not established in adolescent (D) but our findings confirm a similar relationship to adults for cortical excitability and performance under well-rested condition (E). However, our data cannot determine the relationship between cortical excitability and illuminance in this age group. Some of the possible scenarios have been shown (F).

Conclusion

To conclude, we provide evidence that the quality of environmental light affects brain function down to one of its very basic aspects i.e. cortical excitability. Our findings further suggest that the biological effect of light on cortical excitability is different in adolescents and young adults. Therefore, the development of light interventions in this age group, to alleviate part of their common daytime sleepiness for instance, will need fine-tuning geared toward their specific light sensitivities. The interplay between light, cortical excitability, and behavior leads to complex outcomes and our study lays the foundation for further exploration into the neurobiological effects of light on adolescents and its broader implications for cognitive processes.



Chapter 8

Discussion

General Discussion

The human brain's response to light extends beyond vision, involving a complex set of non-visual effects that influence various physiological and behavioral processes such as circadian rhythms, endocrine function, sleep-wake regulation, mood, and cognition (Campbell et al., 2023). These effects are primarily mediated by ipRGCs, which are particularly sensitive to short-wavelength blue light (~480 nm). The ipRGCs' signals reach a range of brain areas, directly and/or indirectly, from the hypothalamus, the primary target of ipRGCs that plays a key role in regulating circadian rhythms and arousal and promoting sleep and wakefulness, to cortical regions that are crucial for controlling various cognitive functions.

The development of electric lighting, particularly the shift from incandescent and fluorescent lights to LEDs, has significantly altered our lighting environment. While earlier light sources had dominant wavelengths closer to 550 nm, LEDs peak around 440-460 nm, with a secondary peak in the yellow-green range. This shift, together with modern lifestyle, have changed patterns of light exposure. People now experience less natural light during the day due to increased indoor activities, and more artificial light at night, particularly from electronic devices like TVs, laptops, phones, and computers. Since most LEDs are enriched in blue light, known for its stimulating NIF effects, these changes have substantial implications for human well-being and performance, with potential adverse effects ranging from sleep disturbances (Chellappa et al., 2013) and cognitive impairments (Vandewalle et al., 2009a) to mood disorders (Bedrosian et al., 2013) and even links to certain cancer pathologies (Garcia-Saenz et al., 2018). Therefore, understanding how the brain responds to light is essential.

While research in rodent models has uncovered extensive neural pathways of the NIF system, translating these findings to humans is challenging. Anatomical differences and the maturation of the human cortex, which supports more complex cognitive functions (Braak and Del Tredici, 2015), complicate direct comparisons. Nonetheless, neuroimaging studies in humans have confirmed that light exposure can affect brain activity in regions involved in circadian regulation, sleep/wake promotion, alertness, executive function and emotional processing (Campbell et al., 2023). Still, the precise mechanism underlying these effects are poorly understood. Additionally, light's effects are not consistent and can be modulated by several factors, including the characteristics of the light, circadian phase (time-of-day), age, and the cognitive tasks being performed at the time of exposure. Understanding the NIF pathways and mechanisms involved as well as the impact of

modulatory factors will be crucial for fully recognizing how light affects various cognitive and physiological processes in humans.

The central theme of this thesis was to first uncover part of the neural mechanisms underlying NIF functions of light. Next, we explored how these neural processes are modulated by external factors.

In this thesis, we aimed to unravel how light influences the brain through a "bottom-up" approach, beginning with the hypothalamus, the primary target of ipRGCs, and progressing through the thalamus, the brain's relay station, to the cortex, where behavior is ultimately expressed. We used advanced techniques, including 7 Tesla fMRI and TMS-EEG, in a multimodal study. Our focus was on how key factors such as light intensity, time-of-day, and developmental stage modulate the NIF effects.

Here, we will discuss the main findings from each of the preceding chapters in greater detail and try to draw conclusions about the broader implications of our studies.

Human Hypothalamus and Its Response to Illuminance

Two studies within this thesis (chapters three and four, published and soon to be submitted, respectively) investigated the hypothalamic response to light. In chapter four we used fMRI to examine the impact of varying illuminance levels on the brain activity of healthy young adults completing auditory working memory and emotional tasks. Results revealed distinct responses across hypothalamic subparts, with increased activity over the posterior hypothalamus and decreased activity over the anterior and tubular hypothalamus at higher illuminance levels.

While the reduced activity in the superior-anterior hypothalamus (which includes the sleep-promoting preoptic area, particularly the VLPO) aligned with our expectations, the decrease in the inferior-anterior hypothalamus, which contains the SCN, contrasted with our hypothesis that light would increase SCN activity, as observed in animal studies (Orlowska-Feuer et al., 2023). We considered two possible scenarios to explain this discrepancy: first, the presence of GABAergic ipRGCs in the SCN, which release the inhibitory neurotransmitter GABA, and second, the limited spatial resolution of fMRI, which prevents us from isolating the SCN, itself. As a result, what we observe may reflect the combined activity of multiple nuclei, rather than solely the SCN. Research has shown that many hypothalamic nuclei exhibit decreased responses to light (personal communication, RJ Lucas), which could help explain our findings.

Consistent with our results, a recent fMRI study using a 3x4x3 mm^3 mask in the inferior-anterior hypothalamus and around the SCN also reported deactivation in response to light

(Schoonderwoerd et al., 2022). If we assume that the SCN is the primary driver of activity in both our inferior-anterior mask and their mask, we might speculate that the neurovascular coupling mechanisms, which link neural activity to local blood flow, could be inverted in this region of the hypothalamus (Drew, 2022; Roy et al., 2021). However, a more recent human perfusion study, using a 2x2x2 mm^3 mask centered on the SCN, found a decreasing trend in SCN activity during darkness, with an increase in activity immediately after the lights were turned on (Oka et al., 2024). This suggests that the inverted neurovascular coupling may not apply to the SCN. Therefore, the most likely explanation for the observed deactivation in our study is the involvement of other hypothalamic nuclei, which could be contributing to this response.

Our analysis of hypothalamic subparts also included the posterior hypothalamus, a region that has received limited attention in chronobiology research. Unlike the anterior hypothalamus, the posterior hypothalamus, which plays a role in promoting wakefulness and contains structures such as the MB, LH and TMN, showed increased activity with higher illuminance levels. To explain this finding, we focused on the role of orexin neurons in the LH. The LH contains two primary types of neurons with opposing actions: orexinergic neurons and melanin-concentrating hormone (MCH) neurons. The activity of orexin-producing neurons is high during wakefulness, while MCH neurons are associated with promoting sleep (Bouâouda and Jha, 2023).

Given the innervation of the LH by ipRGCs (Do, 2019; Hattar et al., 2006; Scammell et al., 2017), we suggest that the increased activity in the posterior hypothalamus may be due to heightened orexin neuron activity in the LH following ipRGC stimulation. This, in turn, could activate wake-promoting regions like the TMN and LC. Research shows that orexin neurons in the LH directly influence the noradrenergic system in the LC, which could enhance LC activity and subsequently impact downstream cognitive processes (Horvath et al., 1999). Specifically, for the emotional task, we propose that the increased activity observed under higher illuminance could directly affect LC functioning.

In the second hypothalamus study (Chapter Five), we shifted our focus to examining how time-of-day and developmental age influence hypothalamic responses to variations in illuminance. The time-of-day comparison was conducted only in adults, and the age group comparison was done only for evening light exposure. All participants completed multiple auditory cognitive tasks during the fMRI scan, with the working memory task being evaluated in this study.

Our results revealed no significant difference in the impact of light exposure at different times of day on hypothalamic responses. This finding may have important implications, as it indicates that the hypothalamus might not be the primary mediator of time-of-day induced differences in NIF

responses, reported in previous studies (Kaiser et al., 2019; Vandewalle et al., 2009a). Instead, other brain regions or mechanisms might be responsible for modulating how light influences the brain at different times of day (e.g. nuclei of the thalamus, cf. next section). Even if the hypothalamus is involved, it is possible that it is not the hypothalamic response itself that varies with time-of-day, but rather hypothalamic connectivity with other brain regions might underlie the observed time-of-day effects. Therefore, a study is needed to investigate the impact of light on connectivity between the hypothalamus and regions like the thalamus or the LC.

Additionally, we compared the hypothalamic responses to evening light in adolescents and young adults. Our findings revealed that adolescents demonstrated a stronger response than adults, with greater deactivation in response to light over the superior-anterior and inferior-tubular hypothalamus. We stress that the difference is not huge as it was only noticeable in the detailed analysis of activity at different illuminance levels. This suggests that the mechanisms through which light affects the brain are likely similar across individuals of all ages, with differences probably being subtle and non-linear. We hypothesized that this heightened response could result from adolescents' increased sensitivity to light, possibly linked to larger pupils and clearer lenses that enhance ipRGC signaling. One could argue that heightened sensitivity to light should also manifest in the inferior-anterior hypothalamus, since this region, which includes the SCN, is a primary target of ipRGCs. Based on our findings, we speculate that the signaling from ipRGCs may exert a more pronounced effect on the superior-anterior hypothalamus, which contains the VLPO, potentially because the superior-anterior region receives direct innervation from ipRGCs and also indirect modulations from the SCN and the LH (Legates et al., 2014; Venner et al., 2019). The more pronounced deactivation seen in the superior-anterior hypothalamus could be associated with age-related differences in the inhibitory responses, potentially in the VLPO. Animal studies suggest that LH-GABA neurons can promote arousal by inhibiting sleep-promoting preoptic neurons, specifically targeting galaninergic VLPO neurons (Venner et al., 2019). Considering that this sleep-promoting area may exhibit a decline in function with age (Singletary and Naidoo, 2011), we can hypothesize that the inhibitory pathway from the LH to the superior-anterior hypothalamus, particularly the VLPO, may differ between adolescents and young adults due to developmental changes, with stronger inhibition observed in adolescents than in adults. Overall, this finding highlights the differences in brain responses attributable to development, which should be considered when designing interventions involving light.

Given the potential heightened activity of orexinergic neurons in the posterior hypothalamus in response to light exposure, one could hypothesize that targeting orexin receptors may be an

ecological/natural way to influence cognitive performance. In other words, to mimic the natural light impact and its beneficial effects on alertness and performance with limited side effects and more ecological outputs, one could focus on increasing orexin signaling. Likewise, one could decrease orexinergic activity to trigger the most effective and natural means to favor sleep for instance. The specificities of for instance adolescents vs. adults would have to be taken into account.

We stress that we are making these assumption and statement about cognition while we did not fully investigate the links between our brain activation findings and performance to the task. In chapter four, we found a negative association between performance and the increased activity in the posterior part of the hypothalamus. It cannot therefore explain the positive impact of light illuminance on performance. This warrant further analyses of our data.

Illuminance and Its Impact on Thalamo-Cortical Connections

In addition to its effects on regional activity, light has recently been identified by our group as a modulator of interregional functional connectivity (Paparella et al., 2023). To investigate this further, in chapter six we examined how light impacts connectivity among the MDN in the thalamus, the SMG in the parietal cortex, and the IFJ in the prefrontal cortex. We focused on three factors that could influence the NIF effects: illuminance level, time-of-day, and age, and we aimed to determine whether and how connectivity would be altered by these variables.

Building on Vandewalle' suggestion that light primarily affects subcortical regions before engaging cortical areas (Vandewalle et al., 2009a), we hypothesized that light would influence bottom-up connectivity, specifically from the thalamus to cortical regions, rather than the reverse. Our findings supported this hypothesis, as we observed no significant effects on cortico-thalamic connectivity under any of the light conditions.

We found that in all groups moderate-intensity blue-enriched light (92 melEDI) and low illuminance orange light modulated the SMG-to-IFJ and the MDN-to-SMG connectivity, respectively.

The modulatory effect of orange light on connectivity was an unexpected finding, especially given our initial hypothesis that NIF effects would be predominantly driven by short-wavelength light. However, as discussed in chapter six, this modulation might have visual origins, possibly related to the role of the MDN in visual processing. Alternatively, this effect could be tied to NIF responses of light itself, as there is evidence suggesting that longer-wavelength light (i.e. orange or red) can

also exert direct NIF effects (Sahin and Figueiro, 2013). While such studies have often been overlooked, they might have more validity than previously thought, indicating that longer wavelengths could influence brain function through non-visual pathways. Furthermore, since ipRGCs receive input from both rods and cones, it is possible that the contribution of these photoreceptors to NIF effects has been underestimated. Another possibility is that the impact of orange light is more about its contrast with darkness and/or white (blue-enriched) light in preceding blocks. Orange light could act as a mild alerting signal, signaling a transition from darkness to light. This relative increase in light exposure might trigger physiological responses associated with arousal and alertness, which in turn could influence the connectivity observed in our study.

Our findings also suggest that both time-of-day and age play significant roles in modulating thalamo-cortical connectivity. Specifically, moderate-intensity blue-enriched light had a more pronounced effect on the MDN-to-SMG connectivity in adolescents, whereas the highest intensity blue-enriched light was more effective in strengthening the MDN-to-IFJ connectivity in the morning compared to the evening.

These results support the heightened sensitivity to light in adolescents, as pointed in one of the hypothalamus studies. To optimize light-based interventions, further studies should focus on understanding how light exposure affects cognitive networks in adolescents during school hours. Specifically, it would be valuable to examine whether, like adults, adolescents may require higher intensity light in the morning for significant cognitive network modulation. This knowledge could then inform the design of classroom environments and educational schedules, using tailored light exposure to enhance cognitive performance and attention in adolescents during their most receptive periods.

Additionally, regarding adults, in the evening, for maintaining optimal cognitive performance, moderate light intensities could be sufficient and should be used. High intensities, on the other hand, may lead to visual discomfort without providing additional cognitive benefits. Of course, all these conclusions require performance analysis, which was not included (yet) in the current study, to fully assess the practical implications of light exposure on cognitive outcomes. An interesting follow-up analysis that could complement this work would involve a similar analysis to the hypothalamus study, but focusing on the ROIs within the network investigated in this study. By assessing how light exposure affects the activity within these ROIs and linking it with connectivity, we could gain deeper insights into the underlying mechanisms. Combining this with our results, we could speculate that the reported increase in prefrontal cortex (PFC) activity in other studies

might be originating from the parietal cortex, which could, itself, be influenced by thalamic activity. Or, for morning exposures, the increase in PFC activity may also be driven directly by thalamic activity itself.

Impact of Illuminance on Electrophysiology: Cortical Excitability

In the final study, chapter seven, we shifted our focus to the cortex to explore how our fMRI findings translate to electrophysiological measures. Using the TMS-EEG technique, we investigated, for the first time, the impact of illuminance on cortical excitability, a fundamental aspect of brain function. Our finding provide the first indication that light can affect cortical excitability. It may therefore tune cortical neuron responses to incoming stimuli and could be part of the mechanisms through which light affects behavior, building on the results discussed in the other chapters.

We compared the effects of light on cortical excitability in young adults and adolescents during the day. While we found no overall differences in cortical excitability between the two groups, the response to three light conditions, differed between the groups. In young adults, the response exhibited an inverted U-shaped function, while adolescents showed no change in cortical excitability across the light conditions, suggesting distinct responses to light in these age groups. This could indicate that adolescents might be more sensitive to light. We imagined several scenarios where this increased sensitivity could lead to no noticeable changes in cortical excitability across different light conditions. Alternatively, they may be less sensitive, leading to an insensitivity in cortical excitability under these conditions. However, given the recommendation for effective light exposure during the day (Brown et al., 2022) (melanopic lux > 250 melEDI) and the fact that both blue light conditions exceeded this threshold, especially high-intensity blue at 625 melEDI, it seems unlikely that cortical excitability would have remained unchanged. We hypothesize that light did influence cortical excitability under both blue light conditions, but due to adolescents' heightened sensitivity, their response might fall at the lower end of the inverted U-shaped curve, leading to no detectable differences in excitability. If our proposed inverted U-shaped function for excitability in response to light holds true, we can conclude that there is an optimal level of light exposure and exceeding this optimal amount may not enhance brain function. Moreover, if our hypothesis about heightened sensitivity to light in adolescents is correct, the optimal light exposure level may differ between adolescents and adults and further studies are needed to determine these optimal levels for each age group.

On the role of ipRGCs

Based on the existing literature, we consider ipRGCs to be the primary drivers of the NIF effects discussed in this thesis. First, studies in rodents show that the hypothalamus, a key structure explored in chapters four and five, receive direct projections from ipRGCs (Do, 2019). Moreover, previous research has demonstrated that blind individuals, who likely have intact ipRGCs but no functional rods or cones, still show preserved NIF responses to light, as evidenced by measures of vigilance, melatonin suppression, and neuroimaging studies conducted in similar contexts to those described in this thesis (Vandewalle et al., 2013; Zaidi et al., 2007). Additional neuroimaging studies have shown that the spectral composition of light significantly influences brain activation, with blue monochromatic light producing a stronger impact on brain activity (Vandewalle et al., 2010, 2007b). One study even highlighted ipRGC-driven brain responses using metameric light (Hung et al., 2017).

Supporting the idea that melanopsin-expressing ipRGCs are the main photoreceptors mediating NIF effects, a meta-analysis revealed that the best predictor of melatonin suppression at light levels above 21 photopic lux was melEDI lux (Giménez et al., 2022). This finding aligns with previous studies and is reinforced by recent work confirming the central role of melanopsin-ipRGCs in regulating several NIF functions, such as circadian phase shifts, melatonin suppression, sleepiness, vigilance, and sleep. Since ipRGCs receive input from rods and cones, their outputs to the brain that would presumably be responsible for the effects we report, could include contribution from classical photoreceptors. A blue-yellow color opposition circuits of cones are relevant for these circadian NIF functions (Blume et al., 2023; Santhi et al., 2012). While ipRGCs are widely recognized as the main contributors to NIF responses to light, the potential role of S-cones remains a subject of debate. S-cones, which are most sensitive to light around 420 nm, overlap with the intrinsic sensitivity range of ipRGCs (Lucas et al., 2014; Wässle, 2004). Some studies have suggested that S-cones contribute to melatonin suppression, while others have found no significant role for S-cones in NIF neuroendocrine or alerting responses (Brown et al., 2021; Spitschan et al., 2019).

Rods, which have peak sensitivity around 507 nm and are mainly involved in scotopic (night) vision, were likely saturated at most of the light levels used in the study and are less likely to have contributed to the results. However, rods do play a role in circadian entrainment in rodents over a broad range of illuminances, suggesting that they may still have some influence on circadian rhythms, even beyond their role in vision (Altimus et al., 2010). We cannot therefore rule out their contribution.

An additional consideration is the variability in the light conditions used across the three experimental chapters. The lower light level differed not only in terms of intensity but also in spectral composition. One light condition was a blue-enriched white light, while another was an orange light. Although we focused on measuring illuminance using melEDI lux, we acknowledge that other classical EDI metrics, such as rhodopic, cyanopic, chloropic, and erythropic EDIs, were not included in our analyses and may also be correlated with our brain measures of interest. The difference in light color may have also triggered part of our findings because of different cone-type involvement or because of more downstream effect of color on brain function.

Limitations

Like any research, the protocols and methods used in this thesis have limitations that should be acknowledged.

fMRI Study

Light Source

A key limitation of the fMRI studies is the challenge in determining which specific light-sensitive photoreceptors in the human retina contribute to the observed NIF responses. Human research is inherently limited in this regard, as one cannot readily manipulate photoreceptor systems in humans in the same way as in rodent models. However, previous neuroimaging studies have often employed monochromatic light sources, which allow for more precise predictions regarding the contribution of specific photoreceptors to NIF effects (Vandewalle et al., 2009a; Vandewalle et al., 2011a, 2010). Here, the decision not to use a monochromatic LED light source was made to better replicate realistic lighting conditions, given the prevalence of polychromatic LED lights in everyday settings. Additionally, the selection of light intensities in our study was influenced by several technical constraints, particularly available equipment and the need to ensure participant comfort throughout the long fMRI scans. Since participants were required to keep their eyes open for the entire duration of the scan, we had to limit the use of very high light intensities, as these could potentially cause discomfort or pain. From our experience, when participants feel discomfort, they tend to move more, which can introduce motion artifacts and degrade the quality of the fMRI signal. Therefore, ensuring a balance between effective light exposure and participant comfort was essential for maintaining data integrity.

It is worth noting that the light intensities used in this study were consistent with those employed in previous neuroimaging studies examining the effects of light on humans (Daneault et al., 2014; Vandewalle et al., 2011a, 2010, 2007a).

Part of the limitation in the maximal illuminance we can administer without causing movement/discomfort may come from the 45-minute dim light adaptation period that participants underwent prior to the fMRI scan. This adaptation likely increased their sensitivity to light and may have altered the contribution of classical photoreceptors to the observed effects. Literature suggests that to effectively isolate the contributions of ipRGCs, it may be beneficial to avoid prior exposure to dim light (Giménez et al., 2022; Lall et al., 2010). A study by my colleague has shown that the 45-minute dim light adaptation in our protocol might indeed affect the results, particularly for lower illuminances (Beckers et al., 2024). To address this, future studies could simplify the light standardization phase by using higher ambient light levels. This would help reducing the contribution of classical photoreceptors and would allow for the use of higher light intensities inside the MRI to more effectively trigger NIF responses and better explore the full spectrum of light's impact on brain activity and function.

Light Sequence

We used short exposure to get a within session design which enhances statistical power. One should also use between session comparison with long exposure as done by our team in their initial studies of the the NIF impact of light in their fMRI studies areas (Vandewalle et al., 2007a, 2006).

A recent publication from our team investigated the potential bias induced by using repeated sequential short-light exposure by investigating the 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 melEDI lux) but at lower irradiances (0.16, 37 melEDI 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. Therefore, short-term prior light history may have potentially biased the results presented in the thesis, through a carry over effect of one block to the next, particularly at lower illuminance. The use of eye-tracking data in the analyses of MRI data may be a way forward to account for this potential bias.

7T MRI

Another limitation we faced in our data analysis relates to the use of ultra-high-field 7T MRI. 7T MRI offers superior resolution and a higher signal-to-noise ratio compared to 3T MRI, allowing for enhanced imaging of subcortical brain regions (Weiskopf et al., 2015). Given the higher number of voxels in 7T MRI, achieving statistical significance could became more challenging due to the issue of multiple comparisons. As a result, we implemented a region of interest approach instead of the whole brain approach. We relied on brain templates to accurately segment brain regions and extract activity estimates, although this process itself is constrained by the specificity of the chosen template. A limitation worth mentioning that is coming to any MRI studies (whether at 7T or at lower field strength), is partial volume effect, where a single voxel may capture signals from multiple adjacent tissue types, leading to blurred boundaries and reduced accuracy in identifying specific subcortical nuclei. In the case of the hypothalamus, the issue is further enhanced by the fact that the different nuclei do not exhibit clear contrast boundaries in MRI signals, making it difficult to isolate and study the nuclei. There have been advancements in the segmentation of subcortical nuclei at 7T MRI, with methods that enhance segmentation precision, potentially benefiting our ability to study small brain regions like the hypothalamus (e.g., (Bazin et al., 2020)). These improvements in segmentation techniques will provide a clearer delineation of nuclei, ultimately improving our understanding of the role of structures like the hypothalamus in light-based interventions and other cognitive functions.

TMS-EEG Study

Semi-Random Order

Since the protocol was quite long (~5 hours), we designed the three light sessions such that we ensured all participants completed at least two TMS-EEG sessions, which was essential for investigating our primary research question: whether blue light affects cortical excitability. This means that the order of sessions was not completely randomized, and the brighter blue light exposure always performed last. Although we accounted for session order in our statistical models, one can argue that we cannot entirely rule out the possibility that the observed decrease in cortical excitability under high melanopic illuminance could be influenced by the time-of-day/order. A previous study has shown that cortical excitability decreases in the evening, particularly during the wake maintenance zone (around the onset of melatonin secretion: 2-4 hours after our protocol) (Ly et al., 2016). This may suggest that the timing of our sessions could have influenced the results,

with the natural circadian variation in cortical excitability potentially interacting with the light exposure effects in ways that were not fully controlled for in our study. However, this speculation may not fully hold up when considering the specifics of prior research. The study reporting a decrease in cortical excitability only measured three time points (11:00, 17:00, and 21:00) within a period from 11:00 to 21:00. They observed a decrease in excitability from 17:00 (almost one hour before the time of our last session) to 21:00, which corresponds to the wake maintenance zone, but they did not measure intermediate time points between 17:00 and 21:00. As a result, we do not know exactly when the decrease in excitability began, leaving this potential timing issue unresolved. Furthermore, if the wake maintenance zone effect were strong enough to counteract the excitability increase induced by light exposure, we would have expected to see its influence reflected in EEG measures, particularly on the alertness index, such as an increase in alpha power or a decrease in theta power, neither of which we observed. Therefore, while time-of-day could have influenced our results, the available evidence does not strongly support this as a major confounding factor.

Short Duration of Wake EEG

Another limitation relates to the EEG measures of arousal. The EEG sessions conducted prior to each TMS-EEG session were relatively short, which may not have provided sufficient time to capture light induced changes in EEG activity. Conducting a longer wake EEG, or a similarly short session also after the TMS when participants had already been exposed to light for at least 15 minutes, could have clarified the potential association between changes in cortical excitability and arousal. One study has proposed an inverted U-shaped relationship between arousal and an indirect measure of cortical excitability, suggesting that exposure to high illuminance can lead to excessive arousal, which may subsequently reduce cortical excitability (Higuchi et al., 1997). This relationship is supported by findings showing that low cortical excitability in high luminance conditions is linked to excessive arousal, as indicated by low relative power of alpha waves. Conversely, low cortical excitability in low luminance conditions corresponds to a low arousal state, reflected by higher relative power of alpha waves. This effect might be particularly relevant in our adolescents group, whose heightened sensitivity to light could result in hyperarousal during light conditions, potentially leading to a lack of significant differences between the blue and orange light conditions.

Baseline Cortical Excitability

Additionally, to make the protocol more feasible for participants , we did not conduct a TMS-EEG session in darkness. Although orange light served as a control condition, the melanopic irradiance was not negligible, leaving open the question of whether the orange light affected cortical excitability. Conducting TMS-EEG in darkness could have improved our ability to interpret the results, particularly in adolescents where no significant differences were observed across light conditions.

There were also some limitations regarding the sample which concern both fMRI and TMS-EEG studies:

Time of Day

For the time-of-day comparison, we only included sessions in the early morning and in the late evening, while including additional times of day would have provided a more comprehensive understanding of the circadian variation in NIF responses to light. But such an approach would have significantly increased the scope of the study and the workload, which is often a limiting factor in PhD projects. However, future studies that are not constrained by such limitations could certainly benefit from including multiple time points throughout the day. By doing so, we could better capture the dynamic changes in brain responses to light and provide more precise insights into the optimal conditions for light exposure based on time-of-day effects.

Additionally, this comparison was only conducted in adults, as we did not have data for adolescents in the morning. If we had been able to include data for adolescents in the morning, it would likely have provided valuable insights into age-related differences in circadian responses to light. However, due to feasibility constraints, discussed before, we were unable to include that session for adolescents in this research.

Differences Between Age Groups

A potential limitation of our age group comparisons is that the age gap between adolescents and adults was not large. It is important to note that safety considerations at the 7T MRI scanner necessitate certain weight requirements for participants. Due to these safety constraints, we chose to include participants aged 15 years and older, ensuring that they met the required safety standards for the high-field MRI procedure. This may have limited our ability to capture more distinct developmental age-related differences in sensitivity to light or neural responses. A larger

gap between adolescents and adults, might have helped identify more pronounced differences in brain activity and light sensitivity. Additionally, we anticipated a difference between age groups in terms of chronotype, with adolescents likely having later chronotypes. However, we ended up having no significant difference in chronotype across the groups. Had we observed later chronotypes in adolescents, it would have been interesting to see how this interacted with light exposure, potentially leading to distinct effects on brain function or behavior.

Socioeconomic Bias

Another limitation regarding our sample is the socioeconomic homogeneity of our sample. All participants came from similar (comfortable/favorable) socioeconomic backgrounds, which is a common bias in research. This lack of diversity in socioeconomic status could limit the generalizability of our findings to broader populations with varying economic circumstances. Socioeconomic status (SES) can potentially influence how individuals experience and respond to light in several ways. For instance, people from lower socioeconomic backgrounds may have less access to well-lit spaces, particularly in terms of natural light. Those in higher SES groups are more likely to live in homes with larger windows, access to outdoor spaces, and work environments with ample daylight exposure, which can influence circadian rhythms and overall well-being. Future studies would benefit from including a more diverse sample to better understand how these factors might influence light exposure effects on brain function.

Statistical Considerations and Interpretation of Non-Significant Results

We emphasize that non-significant effects in our studies do not necessarily imply the absence of an effect. Rather, they may simply indicate that the significant effects were stronger or more detectable. Bayesian statistics could be useful when no significant effect is found, as it allows for estimating the probability of an effect being present. However, it is important to note that Bayesian analysis requires strong evidence to confidently support the absence of an effect. Without such evidence, we cannot draw firm conclusions about its true absence, and we would remain in a similar position to where we are with classical statistics.

Bringing the Pieces Together: Connecting Insights Across Studies

A more general overview of the four experimental studies can be framed within a model that illustrates how the NIF effects of light spread from the retina to the subcortical and cortical regions in humans. The Previous human neuroimaging investigations have provided evidence for the hypothesis that light first influences subcortical regions of the brain, before affecting cortical regions, depending on the ongoing cognitive processing (Gaggioni et al., 2014; Vandewalle et al., 2009a). Our results are roughly consistent with this general view and allow for a more detailed understanding.

To summarize, light first hits the retina and travels to the hypothalamus, and other subcortical regions along the way. From the hypothalamus, the signal reaches the thalamus and other structures like the LC. From there, ultimately, light reaches the cortical brain regions, where it exerts its NIF effects. At the cortical level, and on a more fundamental level, optimal light exposure enhances the responsiveness of neuronal populations to stimuli. This increased excitability likely leads to more efficient information processing and contributes to improved cognition overall.

Finally, our study aimed not only to understand the underlying mechanisms through which light influences brain activity but also to explore how factors such as light intensity, time-of-day, and developmental stage affect the NIF responses. The results underscore that all three factors play a role in modulating NIF responses. However, among these factors, developmental stage provided the most consistent findings, with adolescents showing a distinct responses to light compared to adults in all studies. Although further research is needed to confirm whether this response truly reflects increased sensitivity, it is reasonable to hypothesize that the directionality of the results points towards greater sensitivity in adolescents compared to adults which is in line with literature.

Future Studies

Considering the limitations discussed in this thesis, future research should explore several key areas to deepen our understanding of the NIF effects of light on cognition and brain function.

While this study evaluated the impact of age by comparing adolescents and young adults, it is important to note that age influences NIF effects beyond just developmental stages. Increasing evidence suggests that the NIF effects of light change with aging (Daneault et al., 2018, 2016, 2014). To expand on these findings, we have planed to recruit older adults (ages 60–75) for fMRI assessments. This research could inform the adaptation of lighting environments in hospitals and

care homes, offering non-invasive strategies to enhance the health and well-being of the elderly population (Giménez et al., 2017).

Further exploratory analyses could investigate sex differences in how light impacts NIF responses and cognition. Existing evidence suggests that these effects may vary between sexes (Chellappa et al., 2017), warranting a closer examination in future studies.

Future brain studies should also explore the use of metameric light and/or silent substitution technique to selectively target specific photoreceptor types (Viénot et al., 2012). This approach could deepen our understanding of how different photoreceptors contribute to NIF responses. One of my colleagues is planning an fMRI study using metameric light to compare its effects on young adults and older individuals.

As already stated, another potential direction is the integration of pupillometry into future analyses. Measuring pupil size and its fluctuations in response to light exposure could provide an additional, non-invasive marker of how light interacts with the brain. This approach would not only allow for more precise tracking of brain response in real time but could also help correct for variations in light input due to pupil constriction, ensuring more accurate measurements of light's true effects on neural responses. This could be particularly useful when studying how different intensities or wavelengths of light interact with brain processes, offering deeper insights into the modulation of brain function by light.

Additionally, future studies could expand the range of tasks used. While our study focused primarily on working memory, incorporating a broader set of cognitive tasks (e.g., attention, emotion, decision-making) would help to build a more comprehensive understanding of how light affects higher-order cognitive functions. Moreover, testing different types of light (e.g., varying in intensity, or color temperature) and linking them to specific cognitive outcomes could help fine-tune the optimal light conditions for various tasks or populations.

Another critical step is to include a wider variety of populations, such as patients with neurological or psychiatric disorders. Understanding how light affects individuals with conditions like depression, anxiety, or neurodegenerative diseases (e.g., Alzheimer's) could open new therapeutic possibilities. Many of these conditions are known to be linked with disrupted circadian rhythms, and targeting light exposure could potentially improve both circadian alignment and overall brain function, offering a non-pharmacological treatment approach with minimal side effects.

Lastly, an important step would be to conduct field studies that move beyond the controlled laboratory setting. Real-world studies in natural environments, such as homes, schools, workplaces or care facilities, could provide more ecologically valid insights into how everyday light exposure

affects cognitive performance, mood, and health. Such studies would help us better understand how light influences us in the contexts where we live and work, which is crucial for translating laboratory findings into practical applications.

Looking ahead, as we deepen our understanding of how light impacts brain function and with the integration of field study results, we may begin to see real-world applications that could dramatically improve how we live. Imagine a world where lighting systems are smart enough to adjust automatically to our needs. Devices could monitor our behavior and biological rhythms, providing the right type of light at the right time to enhance alertness, improve mood, and optimize cognitive performance. Such systems could be applied in workspaces to boost productivity, in schools to enhance learning, or in healthcare settings to support recovery and mental well-being.

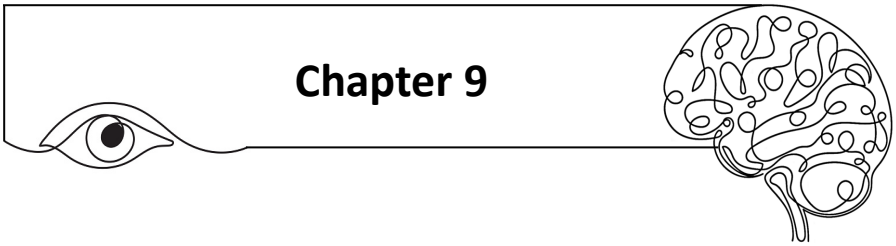
Conclusion

Light is far more than just a means of seeing. It actively shapes our brain function, mood, and cognition in ways we are only beginning to understand. For too long, we've underestimated light's impact, viewing it a passive element that simply sets our circadian rhythms or helps us see. Yet research has now revealed that light plays a far more profound role in how our brains function.

One of the biggest challenges in this field is that light's effects on the brain are subtle, multifaceted, and depend on so many variables, things like age, time-of-day, and the intensity or wavelength of light. It is this complexity that makes understanding light's full potential so difficult. But it also makes our findings even more important.

What's particularly compelling is the potential to apply this new understanding to enhance our environments. Whether in offices, schools, or healthcare settings, adjusting light exposure has the potential to boost cognitive performance, elevate mood, and improve overall well-being. Light, it turns out, has a powerful influence on brain function.

In the end, our research shows that light is much more than a passive background element, it is a driving force in how we perceive and process the world around us. There's still much to discover, but the implications for how we use light in everyday life are profound. The more we understand, the more we can unlock its full potential to transform how we live and work.



Chapter 9

Appendices

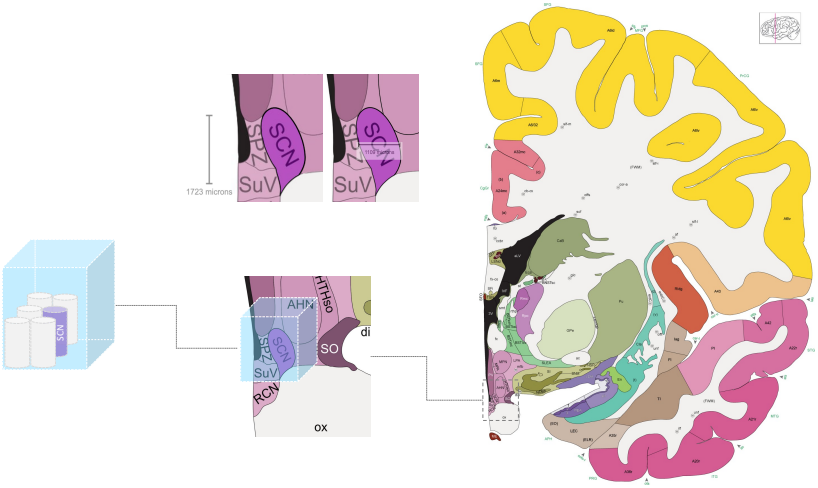
Appendix 1

This appendix is based on our published editorial letter in PNAS:

Sharifpour, R., Campbell, I., Beckers, E., Balda, F., Mortazavi, N., Koshmanova, E., ... & Vandewalle, G. (2022). Pitfalls in recording BOLD signal responses to light in small hypothalamic nuclei using Ultra-High-Field 7 Tesla MRI. *Proceedings of the National Academy of Sciences*, *119*(49), e2212123119.

Pitfalls in recording BOLD signal responses to light in small hypothalamic nuclei using Ultra-High-Field 7 Tesla MRI

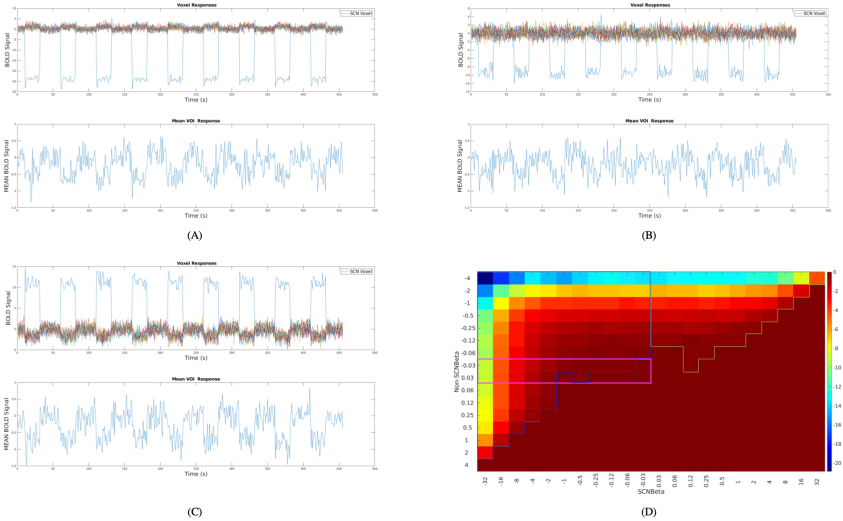
The advent of Ultra-High-Field (UHF) 7-Tesla (or higher) MRI lifted part of the limitations to assess functional responses of small brain structures in vivo. The resolution remains, however, far from invasive techniques applicable in animal models (Barron et al., 2021). Schoonderwoerd et al. recently investigated light response of the anterior hypothalamus using UHF fMRI (Schoonderwoerd et al., 2022). The hypothalamus portion they considered includes the suprachiasmatic nucleus (SCN), which is the site of the master circadian clock and receives strong photic inputs from the retina to contribute to the so-called nonvisual impact of light on physiology (Bumgarner and Nelson, 2021). While we applaud their intentions, we caution that they overlooked the potential limitations of their approach. The authors overstated that they provided functional responses of the SCN itself and delivered potentially erroneous recommendations. The size of the SCN is estimated to be (1.7 × 1.1 × 1.1) mm^3 ~ 2.1 mm^3 (Ding et al., 2016) which is close (but 20% smaller) to the voxel size used by Schoonderwoerd et al. [(1.25 × 1.25 × 1.65) mm^3 ~ 2.6 mm^3]. Because the SCN was most likely partly covered by several voxels, they averaged the blood oxygen level-dependent (BOLD) signal over a (3 × 4 × 3) mm^3 VOI placed around the SCN location (=36 mm^3), i.e., a volume 18 times larger than the SCN. As shown in **Suppl. Figure 9-1**, despite their careful and individually tuned manual placement around the SCN, the VOI undoubtedly contained nuclei surrounding the SCN, several of which also receive retinal inputs (Aranda and Schmidt, 2021) triggering a decrease in their activity (Brown et al., 2011).



Supplementary Figure 9-1 Representation of the SCN size relative to other brain structures.
The (3×4×3) mm³ volume of interest (VOI) used by Schoonderwoerd et al. to extract and average BOLD signal around the SCN. Left: The SCN is estimated to be (1.7×1.1×1.1) mm³ (~2.1 mm³) cylinder that is ~18 times smaller than the 36 mm³ VOI. Middle and Right: The SCN and its surrounding nuclei. Its representation has been zoomed in from the brain atlas displayed on the right).

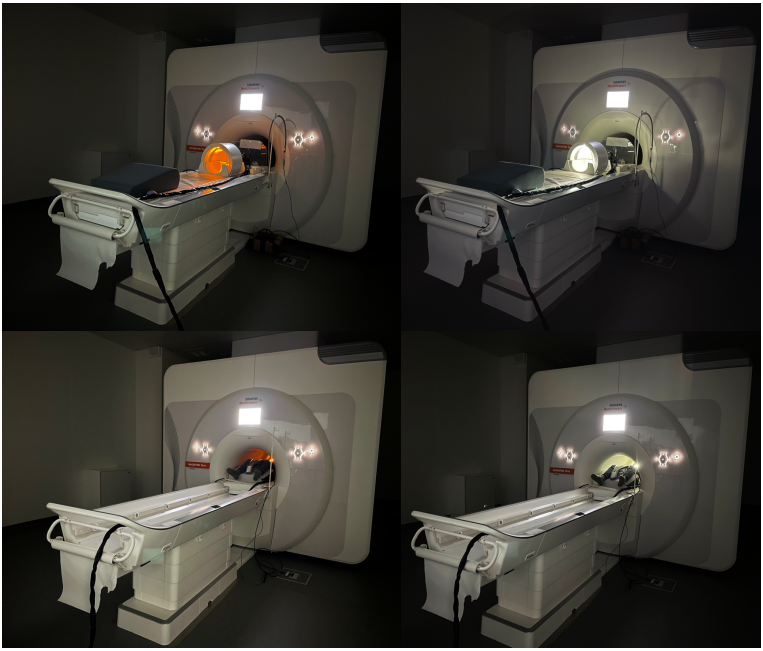
Furthermore, the BOLD signal is inherently smooth, which further increases partial volume effects. The value of a voxel depends therefore on its neighbors and may even be driven by a surrounding nucleus. Even, a local increase in the BOLD value located in the exact location of the SCN would provide support but no proof that the SCN drives the signal. We further estimated that the amplitude of the BOLD signal induced by light should be ~15 times (output of a simulation; the exact value is not known) larger in the SCN than in the non-SCN structures to drive a deactivation over the entire VOI (**Suppl. Figure 9-2**). While this is possible, we show that most scenarios leading to the decrease in the BOLD signal over the VOI include signals from non-SCN structures and the decrease could even result from non-SCN structures showing decreased signals while the SCN presents increased signal (**Suppl. Figure 9-2**). These aspects, and others dealing with the fMRI sequence, statistics, and control procedures that, we detailed here (Sharifpour et al., 2022b), could contribute to the surprisingly reduced so-called SCN response Schoonderwoerd et al. reported in response to light exposures of various wavelengths (λ_{max} : 470, 515, and 590 nm). As established notably by coauthors of Schoonderwoerd et al., the SCN is typically excited by light (Meijer et al.,

1998) particularly if it contains a large portion of blue-wavelength light (~460–480 nm) (Brown et al., 2011). Using positron-emission tomography (PET) in humans, a deactivation following exposure to light was reported around the putative suprachiasmatic area (Perrin et al., 2004). This PET study cannot however be cited to corroborate findings obtained during light exposure. In summary, the study of Schoonderwoerd et al. is truly original and opens interesting questions. Their results should, however, be envisaged with care and cannot be used to recommend therapeutic light intervention.

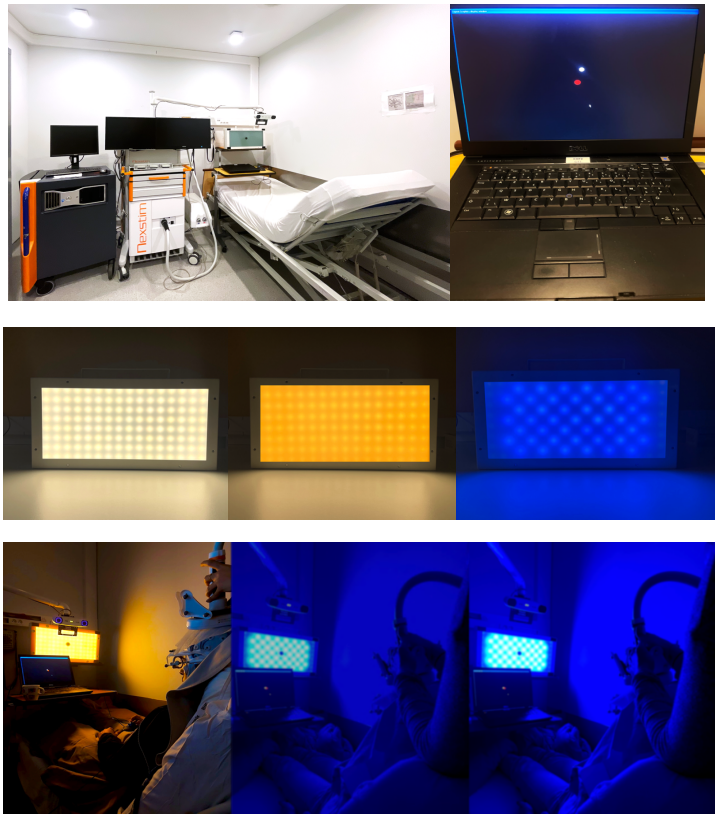


Supplementary Figure 9-2: Simulation of BOLD signal change.
BOLD signal change over a (3 × 4 × 3) mm³ VOI as used by (Schoonderwoerd et al., 2022) to extract and average BOLD signal around the SCN. In the top part of panels A–C, we considered the BOLD signal change in the SCN (blue line), and in 13 surrounding non-SCN voxels, including additive noise, that could result in an overall decrease in BOLD signal when averaged over the VOI as displayed in the bottom parts of panels A–C. (A) The SCN shows a strong deactivation in response to light, while the non-SCN voxels show a slight activation; minimum SCN/non-SCN signal ratio = −15. (B) The SCN shows a strong deactivation in response to light, while the non-SCN voxels show no response; minimum SCN/non-SCN signal ratio = −24. (C) The SCN shows a strong activation in response to light, while the non-SCN voxels show deactivations; minimum SCN/non-SCN signal ratio = −7. (D) t-value map for the average signal using different combinations of beta values of SCN and non-SCN voxels, along the horizontal and vertical axes, respectively (t-values > 0 are set to 0). A limited part of the scenarios corresponds to a decreased response in the SCN with no response in non-SCN surrounding structures (highlighted in purple). A substantial portion of scenarios correspond to diverse degrees of deactivations in SCN and non-SCN voxels (including larger deactivation in non-SCN structures) (highlighted in blue). Another substantial portion corresponds to activation of SCN and deactivations in the surrounding structures resulting in negative average value over the VOI (highlighted in green).

Appendix 2



Supplementary Figure 9-3: fMRI light setup.
Light delivered to the fMRI coil using an 8-m long MRI-compatible dual branched optic fiber.



Supplementary Figure 9-4: TMS-EEG experimental setup.
Participants performed the Compensatory Tracking Task (CTT) on a laptop while undergoing TMS-EEG recording. This task involves tracking a white moving dot with a cursor while a fixed red dot serves as a reference point. The goal is to maintain the white dot as close as possible to the red dot by adjusting the position of the cursor in real time.
The light box used for the study offered two modes: white light, monochromatic blue light, both adjustable in intensity. Orange light was generated by applying an orange film to the box on white mode.

Appendix 3

Supplementary Tables for :

Regional Response to Light Illuminance Across the Human Hypothalamus

Supplementary Table 9-1: Demographics of the first hypothalamus 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 9-2: Light characteristics of the fMRI study.

	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 (589 nm). ipRGCs: intrinsically photosensitive retinal ganglion cells. FWHM: full width at half maximum.

Supplementary Table 9-3: 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

Hypothalamus subpart	illuminance	vs. illuminance	t-value	p-value
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**
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 9-4: 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

Hypothalamus subpart	Illuminance	Vs. illuminance	t-value	p-value
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
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 9-5: Post hoc contrasts between hypothalamus subparts 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

Illuminance	subpart	vs. subpart	t-value	p-value
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
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 9-6: Post hoc contrasts <u>between</u> hypothalamus subparts for each illuminance during the <u>emotional task.</u>

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

Illuminance	subpart	vs. subpart	t-value	p-value
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
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 9-7: 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 4

Supplementary Tables for :

Consistent Regional Hypothalamic Response to Illuminance with Time of Day but not with Developmental Age

Supplementary Table 9-8: Pair-wise comparison of regional hypothalamic response to different illuminance levels in adults.

RESPONSES OF HYPOTHALAMUS SUBPARTS TO EACH ILLUMINANCE

Hypothalamus subpart	Contrast	T-value	P-value
1	0 vs 0.16	0.68	0.50
1	0 vs 37	**3.06**	**0.002**
1	0 vs 92	**2.29**	**0.02**
1	0 vs 190	**4.16**	**<.0001**
1	0.16 vs 37	**2.38**	**0.02**
1	0.16 vs 92	1.61	0.11
1	0.16 vs 190	**3.48**	**0.0005**
1	37 vs 92	-0.77	0.44
1	37 vs 190	1.10	0.27
1	92 vs 190	1.86	0.06
2	0 vs 0.16	0.76	0.45
2	0 vs 37	**2.00**	**0.04**
2	0 vs 92	**2.46**	**0.01**
2	0 vs 190	**2.51**	**0.01**
2	0.16 vs 37	1.24	0.22
2	0.16 vs 92	1.70	0.09
2	0.16 vs 190	1.75	0.08
2	37 vs 92	0.47	0.64
2	37 vs 190	0.52	0.61
2	92 vs 190	0.05	0.96
3	0 vs 0.16	-0.99	0.32
3	0 vs 37	-1.10	0.27
3	0 vs 92	**-2.41**	**0.02**
3	0 vs 190	**-2.79**	**0.005**
3	0.16 vs 37	-0.10	0.92
3	0.16 vs 92	-1.42	0.16
3	0.16 vs 190	-1.80	0.07
3	37 vs 92	-1.31	0.19
3	37 vs 190	-1.69	0.09
3	92 vs 190	-0.38	0.70
4	0 vs 0.16	0.74	0.46
4	0 vs 37	**2.03**	**0.04**
4	0 vs 92	**2.45**	**0.01**
4	0 vs 190	**3.31**	**0.001**

4	0.16 vs 37	1.30	0.19
4	0.16 vs 92	1.72	0.09
4	0.16 vs 190	**2.57**	**0.01**
4	37 vs 92	0.42	0.67
4	37 vs 190	1.27	0.20
4	92 vs 190	0.85	0.39
5	0 vs 0.16	0.32	0.75
5	0 vs 37	1.06	0.29
5	0 vs 92	0.76	0.44
5	0 vs 190	1.38	0.17
5	0.16 vs 37	0.74	0.46
5	0.16 vs 92	0.45	0.66
5	0.16 vs 190	1.06	0.29
5	37 vs 92	-0.29	0.77
5	37 vs 190	0.32	0.75
5	92 vs 190	0.62	0.54

Supplementary Table 9-9: Group comparison of regional hypothalamic response at each illuminance level between adolescents and adults.

GROUP COMPARISON BETWEEN EACH HYPOTHALAMUS SUBPART RESPONSE TO DIFFERENT ILLUMINANCE LEVELS IN ADOLESCENTS AND YOUNG ADULTS

Hypothalamus subpart × Illuminance	Contrast	T-value	$P_{corrected(Tukey)}$
1 0	Adolescents vs Adults	1.02	0.31
1 0.16	Adolescents vs Adults	-0.93	0.35
1 37	Adolescents vs Adults	1.20	0.23
1 92	Adolescents vs Adults	0.47	0.64
1 190	Adolescents vs Adults	-0.92	0.36
2 0	Adolescents vs Adults	1.00	0.32
2 0.16	Adolescents vs Adults	-0.45	0.65
2 37	Adolescents vs Adults	0.17	0.87
2 92	Adolescents vs Adults	-1.07	0.29
2 190	Adolescents vs Adults	-2.01	**0.04**
3 0	Adolescents vs Adults	1.18	0.24
3 0.16	Adolescents vs Adults	1.21	0.23
3 37	Adolescents vs Adults	1.20	0.23
3 92	Adolescents vs Adults	0.03	0.97
3 190	Adolescents vs Adults	-0.28	0.78
4 0	Adolescents vs Adults	-0.16	0.87
4 0.16	Adolescents vs Adults	-0.42	0.68
4 37	Adolescents vs Adults	-0.14	0.89
4 92	Adolescents vs Adults	-0.46	0.64
4 190	Adolescents vs Adults	-2.06	**0.04**
5 0	Adolescents vs Adults	0.90	0.37
5 0.16	Adolescents vs Adults	0.31	0.75
5 37	Adolescents vs Adults	0.42	0.68
5 92	Adolescents vs Adults	-0.65	0.51
5 190	Adolescents vs Adults	-0.86	0.39

***Supplementary Table 9-10: Pair-wise comparison of regional hypothalamic response to different illuminance levels in evening adults* and adolescents.**

GROUP COMPARISON BETWEEN EACH HYPOTHALAMUS SUBPART RESPONSE TO DIFFERENT ILLUMINANCE LEVELS IN ADOLESCENTS AND YOUNG ADULTS

Hypothalamus subpart × Age group	Contrast	T-value	$P_{corrected(Tukey)}$
1 Adults	0 vs 0.16	-0.78	0.43
1 Adults	0 vs 37	1.97	**0.05**
1 Adults	0 vs 92	2.27	**0.02**
1 Adults	0 vs 190	2.93	**0.003**
1 Adults	0.16 vs 37	2.76	**0.006**
1 Adults	0.16 vs 92	3.05	**0.002**
1 Adults	0.16 vs 190	3.71	**0.0002**
1 Adults	37 vs 92	0.30	0.77
1 Adults	37 vs 190	0.95	0.34
1 Adults	92 vs 190	0.66	0.51
1 Adolescents	0 vs 0.16	1.91	0.06
1 Adolescents	0 vs 37	1.78	0.07
1 Adolescents	0 vs 92	3.11	**0.002**
1 Adolescents	0 vs 190	5.72	**<.0001**
1 Adolescents	0.16 vs 37	-0.13	0.90
1 Adolescents	0.16 vs 92	1.20	0.23
1 Adolescents	0.16 vs 190	3.81	**0.0001**
1 Adolescents	37 vs 92	1.33	0.18
1 Adolescents	37 vs 190	3.94	**<.0001**
1 Adolescents	92 vs 190	2.61	**0.009**
2 Adults	0 vs 0.16	-0.11	0.91
2 Adults	0 vs 37	0.94	0.35
2 Adults	0 vs 92	0.75	0.45
2 Adults	0 vs 190	1.10	0.27
2 Adults	0.16 vs 37	1.05	0.29
2 Adults	0.16 vs 92	0.86	0.38
2 Adults	0.16 vs 190	1.21	0.23
2 Adults	37 vs 92	-0.19	0.85
2 Adults	37 vs 190	0.15	0.88
2 Adults	92 vs 190	0.34	0.73
2 Adolescents	0 vs 0.16	1.91	0.06
2 Adolescents	0 vs 37	2.13	**0.03**
2 Adolescents	0 vs 92	3.65	**0.003**

2 Adolescents	0 vs 190	5.33	**<.0001**
2 Adolescents	0.16 vs 37	0.22	0.82
2 Adolescents	0.16 vs 92	1.75	0.08
2 Adolescents	0.16 vs 190	3.42	**0.0006**
2 Adolescents	37 vs 92	1.53	0.13
2 Adolescents	37 vs 190	3.20	**0.001**
2 Adolescents	92 vs 190	1.67	0.09
3 Adults	0 vs 0.16	-0.33	0.74
3 Adults	0 vs 37	-1.15	0.25
3 Adults	0 vs 92	-1.95	**0.05**
3 Adults	0 vs 190	-2.04	**0.04**
3 Adults	0.16 vs 37	-0.81	0.42
3 Adults	0.16 vs 92	-1.62	0.10
3 Adults	0.16 vs 190	-1.70	0.09
3 Adults	37 vs 92	-0.81	0.42
3 Adults	37 vs 190	-0.89	0.37
3 Adults	92 vs 190	-0.08	0.94
3 Adolescents	0 vs 0.16	-0.39	0.70
3 Adolescents	0 vs 37	-1.23	0.22
3 Adolescents	0 vs 92	-0.42	0.67
3 Adolescents	0 vs 190	-0.08	0.94
3 Adolescents	0.16 vs 37	-0.84	0.40
3 Adolescents	0.16 vs 92	-0.04	0.97
3 Adolescents	0.16 vs 190	0.31	0.76
3 Adolescents	37 vs 92	0.80	0.42
3 Adolescents	37 vs 190	1.15	0.25
3 Adolescents	92 vs 190	0.34	0.73
4 Adults	0 vs 0.16	0.34	0.73
4 Adults	0 vs 37	1.15	0.25
4 Adults	0 vs 92	1.51	0.13
4 Adults	0 vs 190	1.446	0.15
4 Adults	0.16 vs 37	0.81	0.42
4 Adults	0.16 vs 92	1.17	0.24
4 Adults	0.16 vs 190	1.12	0.26
4 Adults	37 vs 92	0.36	0.72
4 Adults	37 vs 190	0.30	0.76
4 Adults	92 vs 190	-0.06	0.95
4 Adolescents	0 vs 0.16	0.71	0.48

4 Adolescents	0 vs 37	1.16	0.25
4 Adolescents	0 vs 92	1.98	**0.05**
4 Adolescents	0 vs 190	4.15	**<.0001**
4 Adolescents	0.16 vs 37	0.45	0.65
4 Adolescents	0.16 vs 92	1.27	0.20
4 Adolescents	0.16 vs 190	3.44	**0.0006**
4 Adolescents	37 vs 92	0.82	0.41
4 Adolescents	37 vs 190	2.99	**0.003**
4 Adolescents	92 vs 190	2.16	**0.03**
5 Adults	0 vs 0.16	0.39	0.70
5 Adults	0 vs 37	0.30	0.77
5 Adults	0 vs 92	-0.33	0.74
5 Adults	0 vs 190	0.37	0.71
5 Adults	0.16 vs 37	-0.09	0.93
5 Adults	0.16 vs 92	-0.73	0.47
5 Adults	0.16 vs 190	0.02	0.98
5 Adults	37 vs 92	-0.63	0.53
5 Adults	37 vs 190	0.07	0.94
5 Adults	92 vs 190	0.70	0.48
5 Adolescents	0 vs 0.16	1.23	0.22
5 Adolescents	0 vs 37	0.99	0.32
5 Adolescents	0 vs 92	1.83	0.07
5 Adolescents	0 vs 190	2.84	**0.005**
5 Adolescents	0.16 vs 37	-0.24	0.81
5 Adolescents	0.16 vs 92	0.60	0.55
5 Adolescents	0.16 vs 190	1.61	0.11
5 Adolescents	37 vs 92	0.84	0.40
5 Adolescents	37 vs 190	1.85	0.06
5 Adolescents	92 vs 190	1.01	0.31

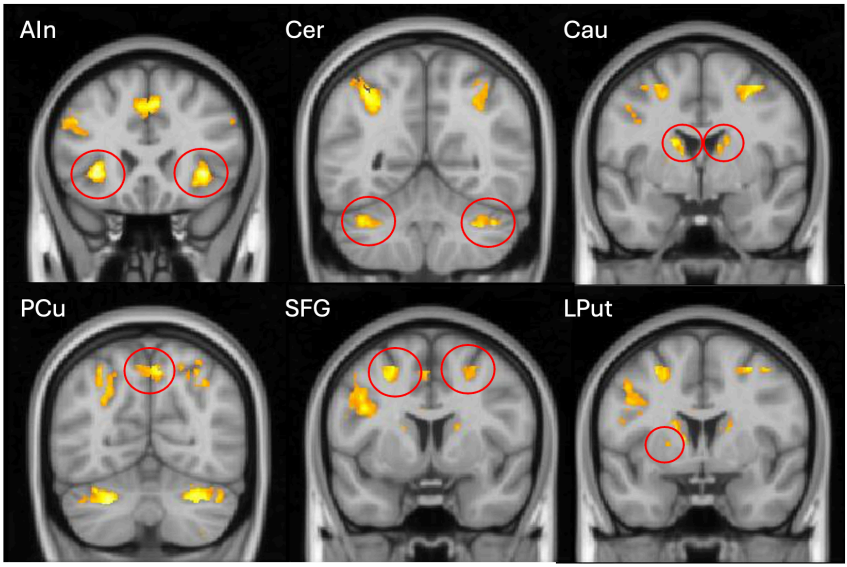
Appendix 5

Supplementary Table and Figure for :

Light Impact on Thalamo-Cortical Connectivity During an Executive Cognitive Task: Effects of Time of Day and Specificities of Teenagers

Supplementary Table 9-11: Activated brain regions in response to the auditory task (contrast: 2-back – 0-back)

Brain area	hemisphere	X,Y,Z	P-value (FWE corrected)
Cerebellum	L	-26, -62, -33	<0.0001
	R	30, -63, -29	<0.0001
Anterior Insula	L	-32, 21, 2	<0.0001
	R	35, 23, -1	<0.0001
Supramarginal gyrus	L	-38, -46,41	<0.0001
	R	42, -42, 45	<0.0001
Inferior frontal junction	L	-47, 10, 32	<0.0001
	R	52, 14, 27	0.004
Thalamus	L	-11, -19, 10	<0.0001
	R	11, -19, 10	<0.0001
Precuneus	L	-5, -65, 54	0.002
	R	5, -65, 50	<0.0001
Superior frontal gyrus	L	-23, 5, 52	<0.0001
	R	25, -2, 54	<0.0001
Caudate	L	-16, -1, 18	<0.0001
	R	17, -4, 20	<0.0001
Putamen	L	-20, 2, 5	0.006



Supplementary Figure 9-5: Brain responses to the N-back task.
Contrast: 2-back vs. 0-back. Bilateral brain activations (P_{FWE} = 0.05) in Anterior Insula (AIn), Cerebellum (Cer), Caudate (Cau), Precuneus (PCu), Superior Frontal Gyrus (SFG) and Left Putamen (LPut).

Appendix 6

Supplementary Method for :

Cortical Excitability is Affected by Light Exposure: Distinct Effects in Adolescents and Young Adults

Experimental Protocol

Prior to the experimental day, participants went through a structural MRI scan using a 7 Tesla MRI scanner (MAGNETOM Terra, Siemens Healthineers, Erlangen, Germany). A T1-weighted MPRAGE image (TR=2300ms, TE=2.76ms, FA=7°, TI=1050ms, bandwidth=240Hz, FoV=256x256x192 mm^3, voxel size=1 mm isotropic spatial resolution) was acquired to use for TMS neuronavigation. Participants were requested to abstain from caffeinated or alcohol drinks and refrain from abnormally intense physical activity for 3 days preceding the study. On the experimental day and to control for recent light history, they stayed in a room equipped with ceiling white LEDs (~180 lux) for 1-hour upon arrival, during which a TMS-compatible EEG-cap was placed. Then they stayed in dim light for almost 1.5h. Three TMS-EEG sessions were performed under different light conditions (**Supple. Table 9-12**), generated by a tunable 35cm×45cm light LED box. The three sessions were separated by at least a 15-minute washout period in dim light (<10 lux) during which participants were allowed to rest while staying on the TMS chair, drink water or have a sugarless snack. Immediately before and after each session, participants reported their sleepiness through the Karolinska Sleepiness Scale (KSS) (Shahid et al., 2012) and rated their motivation, joy, fatigue, stress, anxiety, and effort using the Visual Analogical Scale (VAS).

Supplementary Table 9-12: Detailed characteristics of the light conditions.

	Control Orange	*Active Low Blue*	*Active High Blue*
Illuminance(lux)	30	30	60
Peak Spectral Irradiance (nm)	580	470	470
Melanopic EDI (lux)	23.7	312.2	625.2
Rhodopic EDI (lux)	25.1	217.6	435.2
Cyanopic EDI (lux)	20.3	308.7	617.3
Chlorpic EDI (lux)	28.3	106.8	213.6
Erythropic EDI (lux)	29.1	54.1	108.2
Irradiance (μW/cm²)	9.3	44.7	89.4
Photon Lux (1/cm²/s)	2.63E+13	1.06E+14	2.12E+14
Log Photon Lux (log_{10} (1/cm²/s))	13.4	14.0	14.03

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