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

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Abstract

Light affects not only vision but also attention, alertness, and cognition, primarily through intrinsically photosensitive retinal ganglion cells sensitive to blue-wavelength light. While previous research has shown that light influences brain regional activity, its impact on brain connectivity remains unclear. Using 7-Tesla fMRI, this study examined how light modulates thalamo-cortical connectivity during an auditory executive task involving the thalamus, the prefrontal cortex (in supramarginal gyrus : SMG), and parietal cortex (in the inferior frontal junction : IFJ). Fifty-five participants, including young adults (19-30y: scanned in the morning or evening) and adolescents (15-16y: scanned in the evening), were studied. Across all groups, moderate blue-enriched light strengthened SMG-to-IFJ connectivity, while low-illuminance orange light enhanced thalamus-to-SMG connectivity. High-illuminance blue-enriched light strengthened thalamus-to-IFJ connectivity only in the morning for young adults, while moderate blue-enriched light enhanced thalamus-to-SMG connectivity in adolescents in the evening. These findings suggest that the thalamus plays a key role in mediating light's cognitive effects and timing and age influence non-image-forming responses.

Introduction

Light influences not only the visual system but also non-visual functions, such as physiological, hormonal, and neurobehavioral responses[1–3]. 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[4]. IpRGCs directly project to a wide range of brain structures including the hypothalamus, thalamus, and amygdala (check e.g. ref[1] 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 performance[5–7]. 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[8]. These effects also vary across lifespan[9,10]. In particular, research indicates that adolescents may respond more strongly to light than adults[9].

Several 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[7,11–13] (for a comprehensive review, see ref[1]). 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 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[14] 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[12,13,15]. In support of our hypothesis, we recently showed that during an attentional task, light illuminance influences the connectivity from the thalamus (pulvinar) to intra-parietal sulcus (IPS), key regions to attentional regulation[16]. Whether and how these observations extend to other cognitive domains is not known.

Here, we used 7T fMRI to examine how light influences the effective connectivity within a three-region network that plays crucial roles in various cognitive processes, particularly executive functions, 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)[17–19]. 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. Blue light influenced the network, particularly thalamo-cortical connectivity, more effectively in the morning compared to the evening, and in adolescents compared to adults. Our findings support the hypothesis that blue wavelength light impacts non-visual cognitive functions by modulating task-dependent information flow, particularly from subcortical to cortical regions.

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 (0.16 melanopic equivalent daylight illuminance (mel-EDI)), and three illuminance levels of blue-enriched cool light (37, 92 and 190 mel-EDI) (**Figure 1**).

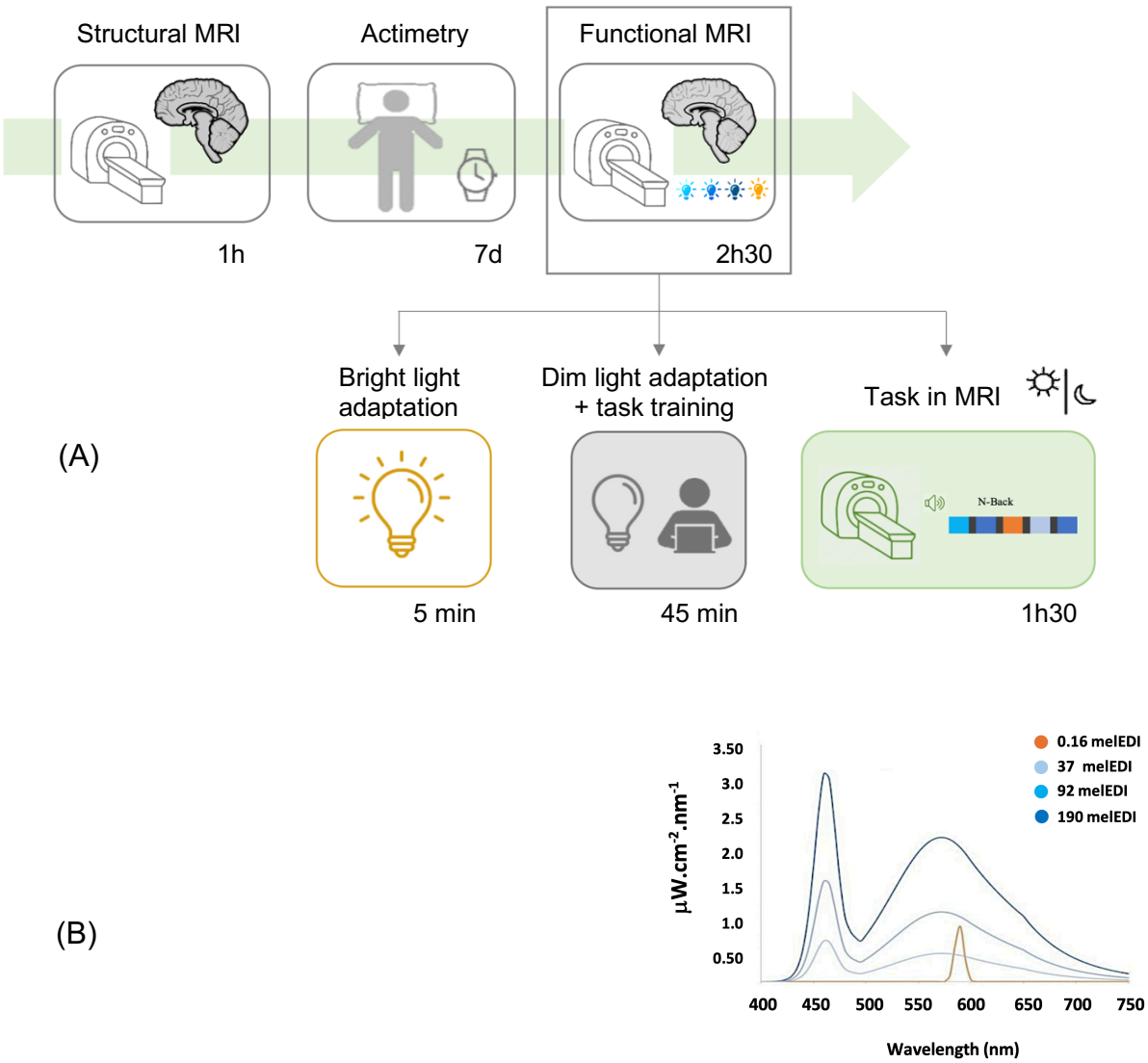


Figure 1:Graphical representation of the experimental protocol (A)*: Participants completed a structural MRI session followed by a functional MRI scan 7 days later, with sleep-wake patterns monitored in between. Before the functional MRI scan, participants were exposed to bright white light for 5 minutes followed by a training session for auditory tasks inside the scanner for 45 minutes in darkness (<10 lux). During the fMRI, they performed a working memory task (N-back) while being exposed to alternating blocks of blue-enriched or orange monochromatic light, separated by darkness periods.*

Spectrum of the 4 light conditions to which participants were exposed during the N-back task (B).

The duration, in days, hours or min of each step is provide below each box. See Table S1 for full light characteristics.

Performance to the 2-back task was good in all participants (mean±SD of accuracy on the 2-back task: 88.2%±9.0% across all subjects; 88.0%±11.0% across adults with morning fMRI; 90.5%±7.5% across adults with evening fMRI and 87.1%±8.2% across adolescents). Importantly, light affected performance on the 2-back task when investigated across all groups ($F(4,208) = 5.55$; **$p = 0.0003$**), with improved accuracy under high illuminance (0.16 & 37 mel-EDI lux < 92 & 190 mel-EDI lux; $t \leq -2.8$; $p < 0.04$) (Figure 2), while there were no difference between age groups and times of day in the impact of light ($F(1,48_{\text{time of day}} / 48_{\text{age-group}}) < 0.05$; $p > 0.9$).

At the brain level, following a standard univariate analysis, we examined how varying illuminance influenced the connectivity between three primary brain regions of interest involved in the task and assessed whether the time of day and age affected the impact of light on connectivity.

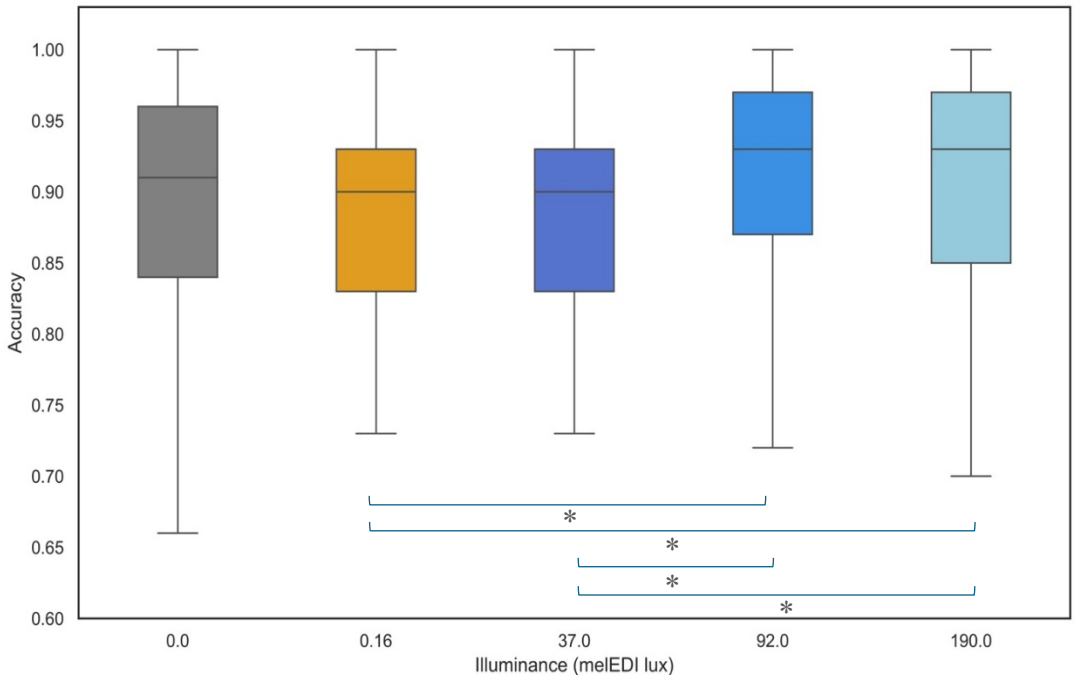


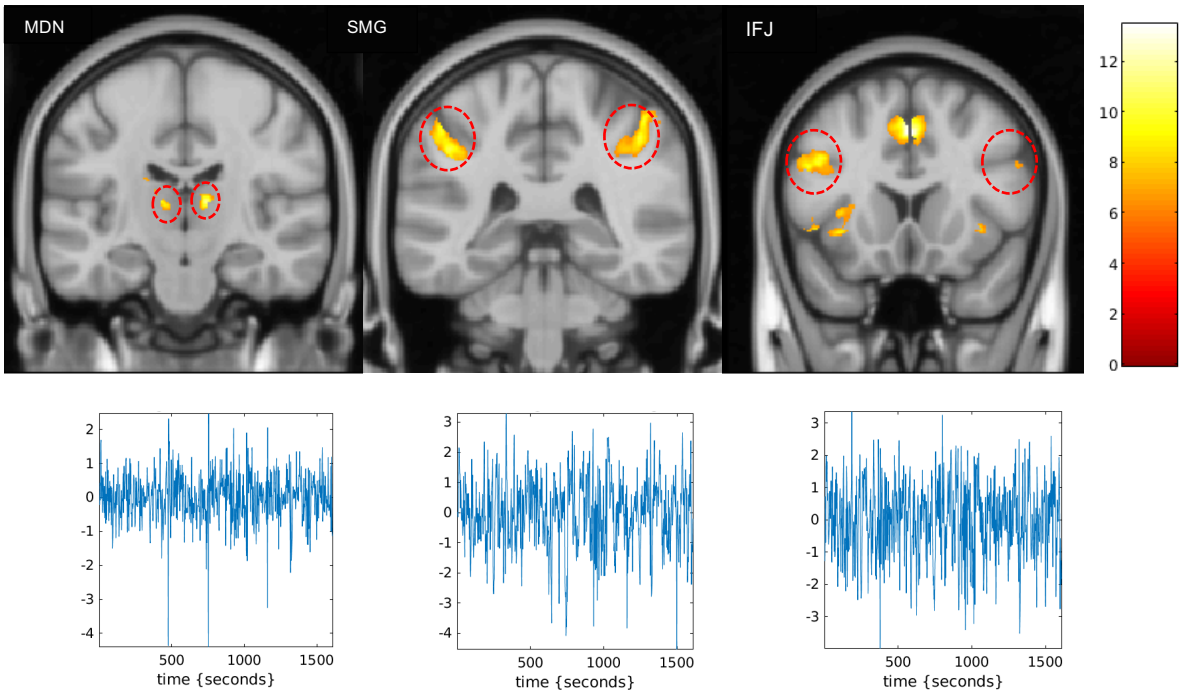
Figure 2: Performance on the 2-back task under each light condition across all groups. Participants showed higher accuracy on the 2-back task under moderate (92 mel-EDI) and high (190 mel-EDI) intensity blue-enriched lights

compared to control orange light (0.16 mel-EDI) and lowest intensity (37 mel-EDI) blue-enriched light [Main effect of illuminance: p= 0.0003]: * p < 0.05 (posthoc contrasts).

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 (Table S1). This analysis confirmed that the task was successful in triggering activation within the thalamus, commonly reported in the context of working memory[39,40], and in the prefrontal and parietal cortices which are typically involved in the verbal n-back task[36–38]. We selected our ROI 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 3-A), as well as the anterior insula and cerebellum (Figure S1). 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 dynamic causal modelling (DCM) to examine the effective connectivity among these three regions under different light conditions in each group of subjects.

(A)



(B)

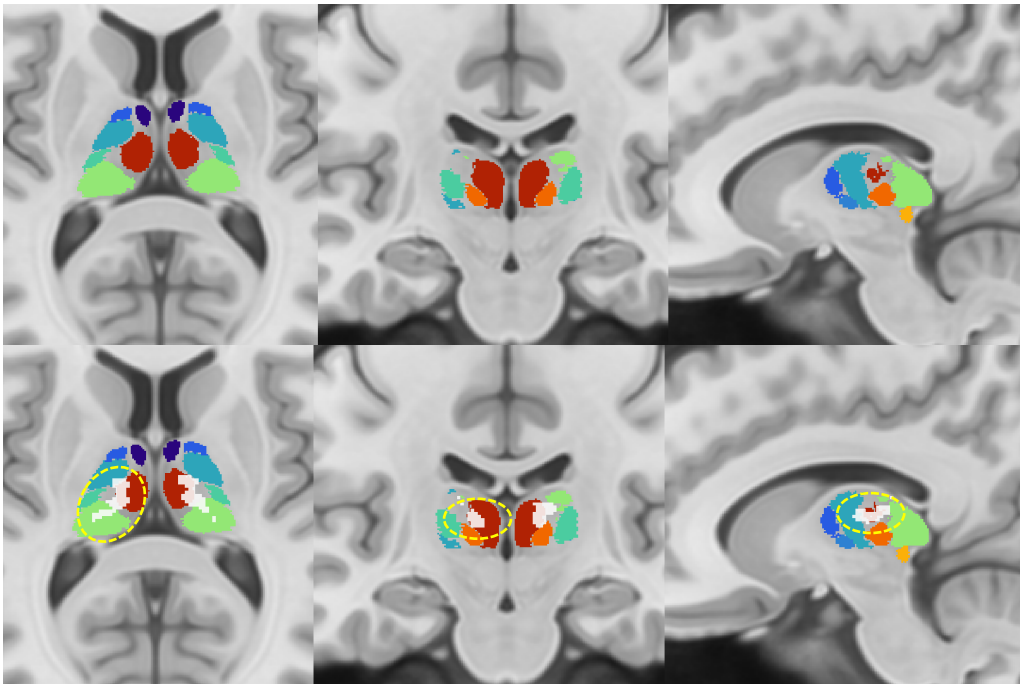


Figure 3. Activation and eigenvariate extracted from the 3 ROIs included in the DCM analysis: A) Left: Bilateral thalamic activation in the mediodorsal nucleus (MDN), Middle: Bilateral parietal activation in the supramarginal gyrus (SMG), Right: Bilateral activation in the inferior frontal junction (IFJ).
B) Top row: Thalamus parcellation map[45]: Maroon: MDN, Orange: Centromedian nucleus (CMN), Light Green: Pulvinar, Yellow: Medial geniculate nucleus (MGN), Turquoise: ventral posterolateral (VPL), Dark Turquoise: ventral lateral posterior (VLp), Royal Blue: Ventral anterior nucleus (VAN), Navy: Anteroventral nucleus (AVN). Habenula, lateral geniculate and ventral lateral anterior nuclei are not visible on the sections shown here. Bottom

row: Thalamic activity overlaid (shown in white) on the parcellation.

Connectivity common to the three group

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 scan in the evening was 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 (in the evening).

DCM analysis in the reference group (Figure 4-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. Interestingly, this means that, 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 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 strong evidence for bilateral connectivity between the MDN and IFJ (Pp=1.0) that indicate 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 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 mel-EDI) blue-enriched light on the connectivity from the SMG to the IFJ. This modulation suggests that under moderate illuminance blue-enriched light condition, the influence of the SMG on the IFJ is increased. Low illuminance orange light (0.16 mel-EDI) showed positive evidence (Pp=0.90) for a strengthening impact on the connectivity from the MDN to the SMG (Figure 4-B). This 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 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 blue-enriched light in the morning (190 mel-EDI) strengthened the connectivity from the MDN to the IFJ, while this effect was not observed in the evening (Figure 4-C). The strengthened 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 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, while this effect was not observed in adults (evening) (Figure 4-D). This 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 the light effects on low illuminance orange light detected in the reference group.

Absence of Link Between Connectivity and Performance in the Morning

In the final step, we further examined whether there was a link between performance and connectivity metrics affected by light in all 3 groups or in the morning vs. the evening and in adults vs. teenagers. We correlated the performance under a given illuminance and a given group with the connectivity value found to be affected by light with positive posterior probability.

Our analysis showed no significant effects of connectivity, time of day, age group or the interaction between connectivity and time of day/age group on performance ($p>0.1$) when focusing on common connectivity modulated by light in all groups (e.g., MDN-to-SMG modulated by orange and SMG-to-IFJ modulated by moderate illuminance blue-enriched light).

When comparing the impact of MDN-to-IFJ connectivity modulated by high illuminance blue-enriched light on performance between morning and evening adults, we found a significant interaction between connectivity and time of day ($F(1,29)=6.34$, $p=0.02$), although the main effects were not significant ($p>0.2$). Post-hoc analysis revealed a positive association between connectivity and performance in the evening group ($t=2.91$, $p=0.007$), but no such association in the morning group ($p=0.28$).

Finally, when comparing the impact of MDN-to-SMG connectivity modulated by moderate illuminance blue-enriched light on performance between adolescents and adults, we observed a statistical trend for the main effect of connectivity ($F(1,28)=3.09$, $p=0.09$), but no significant effects for the age group or the interaction between connectivity and age group ($p>0.19$).

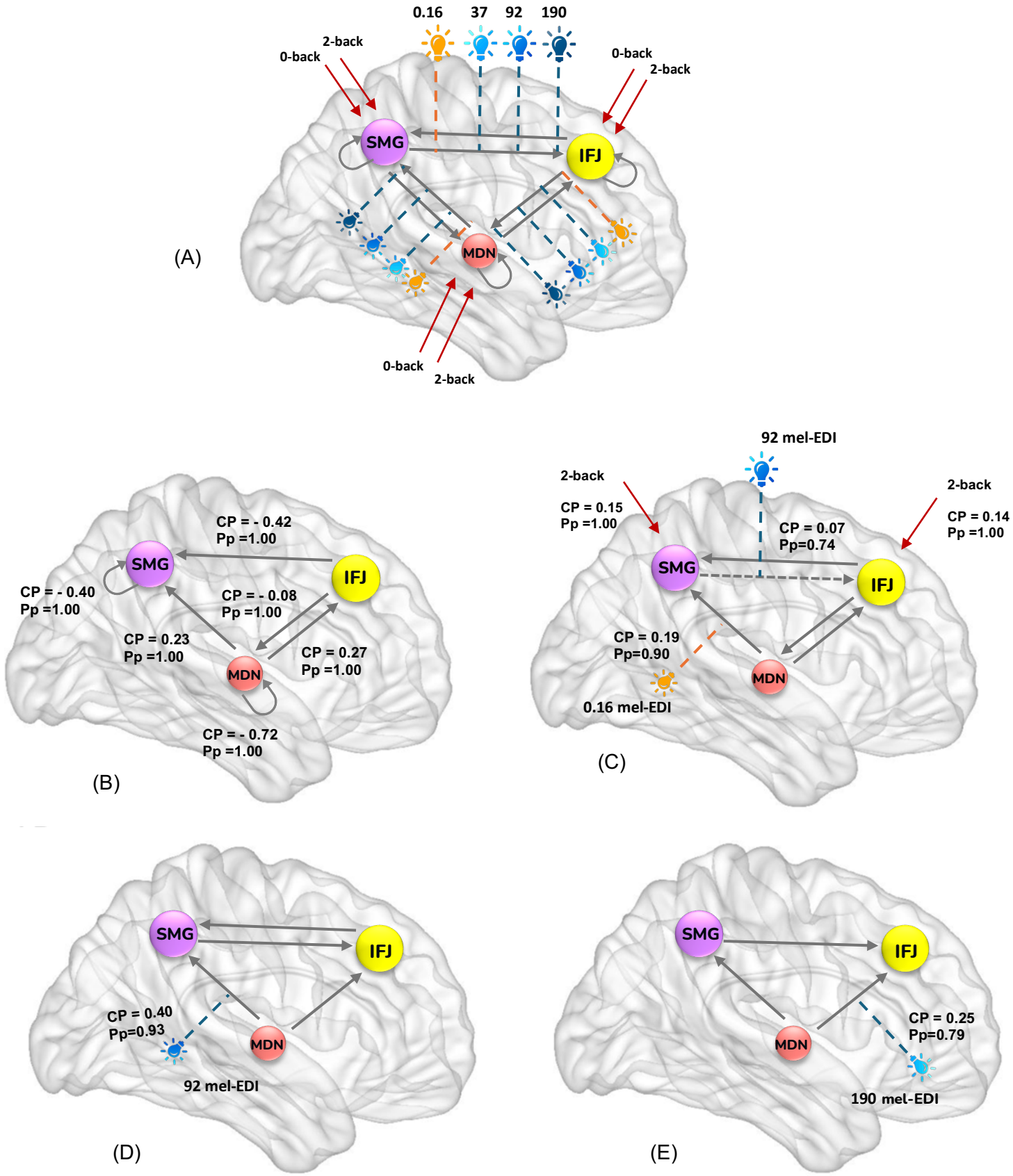

0.16
37
92
190
2-back
0-back
0-back
2-back
SMG
IFJ
MDN
(A)
0-back
2-back
CP = - 0.42
Pp =1.00
SMG
IFJ
CP = - 0.40
Pp =1.00
CP = - 0.08
Pp =1.00
CP = 0.23
Pp =1.00
CP = 0.27
Pp =1.00
MDN
CP = - 0.72
Pp =1.00
(B)
92 mel-EDI
2-back
CP = 0.15
Pp =1.00
2-back
CP = 0.14
Pp =1.00
CP = 0.07
Pp=0.74
SMG
IFJ
CP = 0.19
Pp=0.90
MDN
0.16 mel-EDI
(C)
SMG
IFJ
CP = 0.40
Pp=0.93
MDN
92 mel-EDI
(D)
SMG
IFJ
MDN
CP = 0.25
Pp=0.79
190 mel-EDI
(E)

Figure 4. Effective connectivity results: A) initial model tested using the DCM framework. B) Baseline (intrinsic) connectivity parameter (CP) common to all groups, as isolated in the reference group (i.e. Adults with fMRI in the evening) C) Modulatory impact of light conditions on connectivity along with tasks' input in the reference group (common to all groups). 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; mel-EDI: melanopic equivalent daytime illuminance. Pp: posterior probability of the parameters. SMG: supramarginal gyrus. Grey arrows: between regions and self-inhibitory connectivity parameters; red arrow: task inputs parameters; colored light bulb: modulatory parameter by light [orange: 0.16 mel-EDI; light blue: 37 mel-EDI; medium blue: 92 mel-EDI; dark blue: 190 mel-EDI.

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 and 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 levels of 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 blue-enriched light 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[12,13,15]. 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[16]. Focusing on executive functions in the context of an auditory n-back task, our current univariate analyses pointed towards the MDN, which is more anterior 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[16]. Likewise, the current thalamus ROI was focused on the MDN but extended dorsally to include a small portion of the pulvinar. Both studies 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 associative nucleus (not only relaying sensory information to the cortex) and it is important for executive functions such as attention, working memory and decision making[46–48]. It is therefore in a good position to convey the stimulating influence of light to the cortex.

Our univariate analyses 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[18]. As part of the parietal lobe, the SMG is involved in the phonological loop[18,49] 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 prefrontal cortex is a key structure for cognitive control, particularly in tasks that demand executive functioning involving decision-making such as the n-back task[19]. It helps with managing information retrieval and update. The thalamus to IFJ connectivity 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[50]. While a classical

response on rods is less likely, it cannot be ruled out[51].

The impact of moderate illuminance blue-enriched light 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[52]. 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.

Surprisingly, we further 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 therefore a direct involvement of rods and/or cones that would trigger a visual response ultimately affecting the crosstalk between the MDN and the 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[53], the ventral LGN (the intergeniculate leaflet in rodents)[54] or directly through the pulvinar[55]. IpRGCs signalling 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[20] as well as through the locus coeruleus (LC) which received indirect inputs from the suprachiasmatic nucleus, 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 found that in the morning, the highest illuminance blue-enriched light affected 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[16]. 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[56]. 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 blue-enriched light 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[8] 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.

Critically also, when comparing age groups, we found that moderate illuminance blue-enriched light increased 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 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[14]. This may be important given the current concerns regarding adolescents using LED screen devices, particularly in the evening[57]. 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[58,59].

The age-group difference we detected may, however, also arise from differences in maturation or wiring of the brain which is considered to be fully completed by age 25y[60]. 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. We further note that the fact that only the moderate illuminance blue-enriched light affected the MDN-SMG connectivity may be an inverted-U shape rather than a ceiling effect this time as higher intensities do not yield additional effects in either age groups.

Future studies with more light conditions and comparing age groups at different times of day are needed to test the hypotheses 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 mel-EDI lux), in the evening (10 mel-EDI lux) and at night (darkness:1 mel-EDI lux) to enhance physiology, sleep quality, and wakefulness in healthy adults[3]. The highest illuminance we administered was 190 mel-EDI 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 mel-EDI lux and impacted connectivity in all groups (particularly in adolescents), confirming also that higher illuminance than recommended for the evening can affect brain functions.

Concomitant to the changes we reported at the level of the brain, light illuminance affected performance on the task, with better accuracy under higher illuminance. We posit therefore that the changes in connectivity triggered by light underlines part of the behavioral changes. However, we did not consistently observe a direct link between task accuracy and the connectivity metrics influenced by light, which prevents us from confidently confirming this hypothesis.

Given the absence of difference in performance under the highest intensity blue light between morning and evening adults, the link between connectivity and performance under the highest intensity blue light that was found only in the evening group may reflect the role of

neurophysiological states in how connectivity translates into behavior. For example, higher levels of alertness or arousal in the morning could make performance less dependent on connectivity strength.

Focusing on evening groups, i.e. adolescents and adults with evening fMRI, an association between connectivity and performance under moderate illuminance blue-enriched light was found, though it did not reach significance level. This trend could suggest that the link between connectivity strength and performance in the evening under lower illuminance light may not be very strong, and a larger sample size might be required to uncover this more clearly.

All these behavioral findings remind us that behaviour depend on complex interaction between (cortical) region of a much larger network than the one we focussed upon in the present study and warrants future, more complex connectivity investigations.

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[1].

Material and Method

This study is part of a larger study that has resulted in several publications using different participant subsets[16,20–22]. 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 February 2021, and September 2023, a total of 55 healthy volunteers aged 15 to 30 years (22.0 ± 4.6y, 29 Females) participated in the study, including 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)[23], mood (21-item Beck Depression Inventory-II)[24], sleep quality (Pittsburgh Sleep Quality Index)[25], daytime sleepiness (Epworth Sleepiness Scale)[26], Insomnia, (Insomnia Severity Index)[27], chronotype (Horne-Östberg)[28], and seasonal changes in mood and behavior (Seasonal Pattern Assessment Questionnaire)[29]. Table 1 summarizes the demographic characteristics of the participants.

***Table 1**. Demographic characteristics of the participants included in the analyses.*

	Adults_Evening (AE)	Adults_Morning (AM)	Teenagers (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 included participants 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 during adolescence, all teenagers 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 short-term prior-light exposure, 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 the executive task (n-back task) on a laptop (Figure 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 33 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 mel-EDI lux),

or a control monochromatic orange light (590 nm; 0.16 mel-EDI lux), to which ipRGCs are nearly insensitive (**Figure 1**). 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 using the same task (between ~10^{12} and 10^{14} ph/cm²/s)[15,30,31] . The orange light was introduced as a control visual stimulation for potential secondary whole-brain analyses. For the present analyses, we discarded colour differences between the light conditions and only considered illuminance as indexed by mel-EDI lux, constituting a limitation of our study. The detailed methodology for the light set-up and its delivery into the MRI scanner can be found in our previous publication[16]. 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)[32].

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 transmit, and a 32-channel receive 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[33]. 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[34]. 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 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 ($1\times1\times1$ mm^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 light illuminance measured in mel-EDI 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), 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 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 in the MFG. 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[35]. 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[36–38]. Additionally, thalamus involvement is commonly reported in the context of working memory[39,40]. 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 (in MNI space), which was thresholded at $p = 0.05$ uncorrected. 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[41].

Effective Connectivity Analysis and Statistics

DCM framework[41], 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 trials as two separate driving inputs, as well as blocks representing the four light

conditions (including the control orange light and blue-enriched cool light at three different mel-EDI 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 4-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[42,43] 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 with at least positive evidence i.e. posterior probability (Pp) exceeding 0.73 (according to ref[44], positive Pp: 0.73-0.95, strong Pp: 0.95-0.99, or very strong Pp > 0.99).

A Generalized Linear Mixed Model (GLMM) was first applied using SAS 9.4 (SAS Institute, NC, USA) to assess the impact of light conditions on task performance, irrespective of connectivity. In this model, task accuracy was the dependent variable, with subject (intercept

and slope) effects included as a random factor. Light conditions (five illuminance levels) were treated as repeated measures with an autoregressive correlation structure of type 1 (AR(1)). The fixed effects included the following predictors: light illuminance, age group, time of day, and covariates including sex and BMI.

A second set of GLMMs was used to determine whether light-modulated connectivity influenced task performance. In these models, task accuracy under the specific lighting condition that modulated connectivity was the dependent variable, with subject (intercept and slope) effects as a random factor. The independent variables included modulated connectivity, age group, and/or time of day, depending on the specific connectivity being analyzed. Sex and BMI were included as covariates of no interest.

All models were adjusted to account for the distribution of the dependent variables. Tukey adjustment was applied to direct post hoc tests of the primary analysis to correct for multiple comparisons. Participants with task accuracy below 65% were excluded from behavioral analyses (2 individuals).

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Author Contributions

R.S., I.C and G.V. designed the research. R.S., J.F.B.A., I.C, I.P, E.B, acquired the data. N.M, E.K, F.B, C.F, P.T, L.L and M.Z provided valuable insights while acquiring, interpreting, and discussing the data. R.S. analyzed the data supervised by G.V. R.S. and G.V. wrote the paper. All authors edited and approved the final version of the manuscript.

Competing Interests

The authors declare no competing interests.

The protocol was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège and all participants received monetary compensation for their participation.

Data availability statement

The processed data and analysis scripts supporting the results included in this manuscript are publicly available via the following open repository: https://gitlab.uliege.be/CyclotronResearchCentre/Public/xxxx (the repository will be created following acceptance / prior to publication of the paper). The raw data could be identified and linked to a single subject and represent a large amount of data. Researchers willing to access to the raw data should send a request to the corresponding author (GV). Data sharing will require evaluation of the request by the local Research Ethics Board and the signature of a data transfer agreement (DTA).

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