Regional response to light illuminance across the human hypothalamus

Islay Campbell[1#], Roya Sharifpour[1#], Jose Fermin Balda Aizpurua[1], Elise Beckers[1,2], Ilenia Paparella[1], Alexandre Berger[1,3,4], Ekaterina Koshmanova[1], Nasrin Mortazavi[1], John Read[1], Mikhail Zubkov[1], Puneet Talwar[1], Fabienne Collette[1], Siya Sherif[1], Christophe Phillips[1], Laurent Lamalle[1], Gilles Vandewalle[1]

[1]GIGA-Cyclotron Research Centre-In Vivo Imaging, University of Liège, Liège, 4000 Belgium

[2]Faculty of Health, Medicine and Life Sciences, School for Mental Health and Neuroscience, Alzheimer Centre Limburg, Maastricht University, Maastricht, 6229 ER The Netherlands.

[3]Institute of Neuroscience (IoNS), Department of Clinical Neuroscience,Université Catholique de Louvain (UCLouvain), Woluwe-Saint-Lambert, 1200 Belgium.

[4]Synergia Medical SA, Mont-Saint-Guibert, 1435 Belgium.

[#] shared first authorship

*Corresponding author: Gilles Vandewalle, GIGA-Cyclotron Research Centre-In Vivo Imaging, Bâtiment B30, 8 Allée du Six Août, University of Liège-Sart Tilman, 4000 Liège, Belgium.

Email: gilles.vandewalle@uliege.be

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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 find that, during both the executive and emotional tasks, higher illuminance triggered an activity increase over the posterior part of the hypothalamus, which includes part of the tuberomamillary nucleus and the posterior part of the lateral hypothalamus. In contrast, increasing illuminance evoked a decrease in activity over the anterior and ventral parts of the hypothalamus, encompassing notably the suprachiasmatic nucleus and another part of the tuberomammillary nucleus. Critically, performance of the executive task was improved under higher illuminance and was negatively correlated with the activity of the posterior hypothalamus area. These findings reveal the distinct local dynamics of different hypothalamus regions that underlie the impact of light on cognition. They may suggest that light acts on the orexin and histamine system to affect the quality of wakefulness.

51 **Introduction**

52 Light exerts multiple non-image-forming (NIF) biological effects that influence the quality
53 of sleep and wakefulness, and higher illuminance is known to stimulate alertness and
54 cognition.[1] The biological effects of light primarily rely on a subclass of retinal ganglion
55 cells that are intrinsically photosensitive (ipRGCs) because they express the photopigment
56 melanopsin, which is maximally sensitive to photons with wavelength ~480nm. IpRGCs
57 combine the light signalling of rods and cones to their intrinsic photosensitivity and,
58 collectively, the biological effects of light present a maximal sensitivity to the shorter blue
59 wavelength of visible light.[2] IpRGCs project to multiple subcortical brain areas and their
60 denser projections are found within the hypothalamus, particularly in nuclei involved in
61 sleep and wakefulness regulation.[2,3] The suprachiasmatic nucleus (SCN), which is the site
62 of the principal circadian clock, receives the strongest inputs from ipRGC inputs, over the
63 anterior part of the hypothalamus.[4] Other nuclei also receive ipRGC projections: the
64 subparaventricular zone, one of the main output routes of the SCN, the ventrolateral
65 preoptic nucleus (VLPO) and the preoptic nucleus (PON), involved in sleep initiation and
66 also found in the anterior part of the hypothalamus; the lateral hypothalamus (LH), site
67 of the orexinergic wake-promoting neurons and melanin-concentrating hormone sleep-
68 promoting neurons, found in contrast over the lateral and posterior parts of the
69 hypothalamus.[2,3]

70 The brain circuitry underlying the biological effects of light has mostly been
71 uncovered in nocturnal rodent models.[1,2] Translation to diurnal human beings, where the

72 later maturation of the cortex allows for complex cognitive processing,[5] remains scarce.
73 In particular, whether hypothalamus nuclei contribute to the stimulating impact of light
74 on cognition in humans is not established.

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

88 **Results**

89 Twenty-six healthy young adults (16 women; 24.3 ± 2.9 y; **Suppl. Table S1**) completed two
90 auditory cognitive tasks encompassing, respectively, the executive[6] and emotional[7]
91 domains, while alternatively maintained in darkness or exposed to short periods (< 1 min)
92 of light of four different illuminances (0.16, 37, 92, 190 melanopic equivalent daylight

illuminance - mel EDI- lux; **Suppl. Table S2**) [**Fig. 1**]. The hypothalamus of each participant was segmented into 5 subparts – inferior-anterior, superior-anterior, inferior-tubular, superior-tubular, and posterior [**Fig. 2A**] – 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.

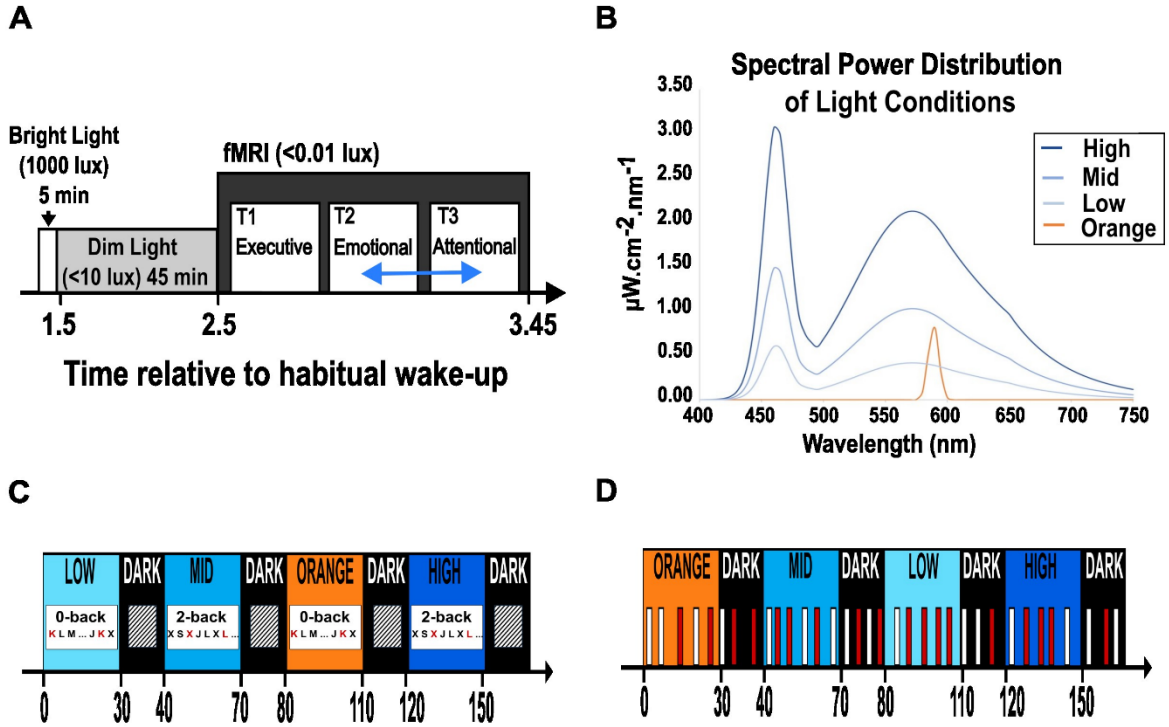

Figure 1. Experimental protocol.
(A) Overall timeline. After prior light history standardisation, participants performed executive (always first), emotional and attentional tasks (pseudo-randomly 2nd or 3rd, blue arrow). As the attentional task included fewer light conditions, it is not considered in the present manuscript (see methods for more details)
(B) Spectral power distribution of light exposures. Monochromatic orange: 0.16 mel EDI lux; Polychromatic, blue-enriched light (6500K); LOW, MID, HIGH: 37, 92, 190 mel EDI lux. For the present analyses, we discarded colour differences between the light conditions and only considered illuminance as indexed by mel EDI lux, constituting a limitation of our study. See Suppl. Table S2 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).

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 [**Fig.2 B-C, Table 1**]. For both tasks, there was no significant main effect for any of the covariates and post hoc analyses showed that the index of the illuminance impact was consistently different in the posterior hypothalamus subpart compared to the other subparts [$p_{corrected} \leq 0.05$, except for the difference with superior tubular hypothalamus subpart during the emotional task: $p_{corrected} = 0.09$; **Table 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 [**Fig. 2 D-G**]. This shows that our results do not come from a relatively unspecific and widespread increase in BOLD signal surrounding the hypothalamus subparts and that the effect of light was most prominent over the posterior and inferior-anterior subparts.

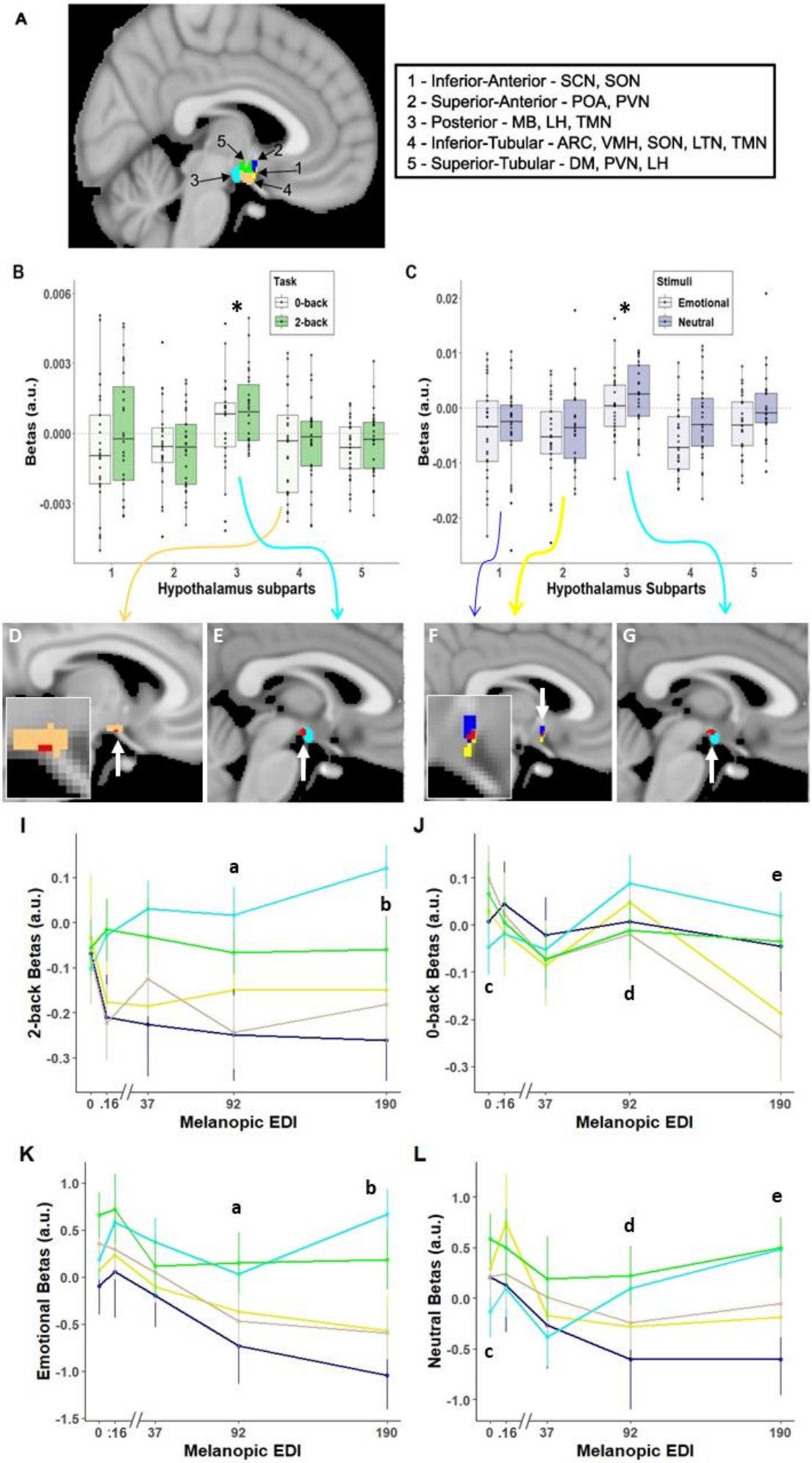
A
1 - Inferior-Anterior - SCN, SON
2 - Superior-Anterior - POA, PVN
3 - Posterior - MB, LH, TMN
4 - Inferior-Tubular - ARC, VMH, SON, LTN, TMN
5 - Superior-Tubular - DM, PVN, LH
B
Task
0-back
2-back
Betas (a.u.)
Hypothalamus subparts
C
Stimuli
Emotional
Neutral
Betas (a.u.)
Hypothalamus Subparts
D
E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

Figure 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 [8]. 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** full statistics)

(B) Executive task: significant main effect of hypothalamus subparts (p=0.002), no significant main effect of task type (p=0.4) or subpart-by-task-type interaction (p=0.61).

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

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

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

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

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

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

(I-L) Estimates of the impact of each illuminance on the activity of the hypothalamus subparts. (Refer for **Table 2** and **Suppl. Tables S3-S7** for full statistics)

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

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

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

178 This prompted us to assess the activity of the hypothalamus subparts under each
179 illuminance to detail the different regional activity dynamics across the hypothalamus.
180 The statistical analyses confirmed that the activity dynamics across illuminance levels
181 differed between the 5 subparts during the executive and the emotional tasks (GLMM;
182 subparts-by-illuminance interaction; $p = 0.041$) tasks [**Fig. 2 I-L; Table 2**]. Post hoc
183 contrasts first considered the impact of the changes in illuminance within each subpart
184 (**Suppl. Tables S3-4**). The activity of the posterior hypothalamus subpart significantly ($p <$
185 0.05) increased under the highest illuminance (190 mel EDI) compared with darkness for
186 both tasks and with the lower illuminances (37 and 92 mel EDI lux) for the emotional task.
187 In contrast, for both tasks, the activity in the inferior-anterior and inferior-tubular
188 hypothalamus subparts significantly ($p < 0.05$) decreased under the highest illuminance
189 compared with darkness, and with lower illuminances for the emotional task. Finally, the
190 activity of the superior anterior hypothalamus subpart decreased under higher
191 illuminance during the emotional but not the executive task, while the activity of the fifth
192 hypothalamus subpart, the superior tubular subpart, was not significantly affected by
193 illuminance changes in either task.

194 Post hoc analyses also yielded several significant differences between
195 hypothalamus subparts ($p < 0.05$) (**Table 2; Suppl. Tables S5-6**). For both tasks, the activity
196 of the posterior hypothalamus subpart was consistently significantly higher than the

activity inferior-tubular subpart under the highest illuminances (92 and 190 mel EDI lux). For the executive task, the activity of the posterior hypothalamus subpart was also significantly higher than the superior-anterior subpart under the highest illuminances (92 and 190 mel EDI lux). For the emotional task, the activity of the posterior hypothalamus subpart was also significantly higher than the superior-anterior subpart under the highest illuminances (190 mel EDI lux), while the activity superior-tubular hypothalamus subpart was significantly higher than the activity of the inferior-tubular, inferior-anterior and superior-anterior hypothalamus subparts (92 and/or190 mel EDI lux).

The overall picture arising from these comparisons is that higher illuminance increased the activity of the posterior and superior hypothalamus subparts while it decreased the activity of the inferior and anterior hypothalamus subparts.

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

Following these analyses, we explored whether the changes in activity across illuminances were related to cognitive performance. We first considered the more difficult (2-back) subtask of the executive task as it requires higher cognitive functions (see method for a full rationale).[6] 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 = 0.1; **Fig. 3A**), 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

218 hypothalamus subpart (GLMM; main effect of posterior subpart activity; F = 9.43; **p =**
219 **0.0027**; Partial R^2 = 0.09). Surprisingly, the association was negative (**Fig. 3B**), suggesting
220 that the part of variance explained by the hypothalamus subpart is distinct from the
221 impact of light on performance. In contrast, no significant association was found when
222 considering the activity of the other four subparts (GLMM; main effect of posterior
223 subpart activity; F < 0.62; p > 0.4; **Fig. 3 C-D, Suppl. Table S7**). We went on and found that
224 the accuracy to the simpler control subtask of the executive tasks (0-back, see method)
225 was not associated with the activity of the posterior hypothalamus subpart (GLMM
226 controlling for age, sex and BMI; main effect of subpart activity; F = 0.57; p = 0.45; **Fig.**
227 **3E**), suggesting that the association with performance is specific to the 2-back subtask.

228 In the last step, we explored the reaction times during the emotional task
229 (accuracy to the lure task is not meaningful). We found that reaction times to the
230 emotional stimuli were not significantly affected by illuminance (GLMM controlling for
231 age, sex and BMI; main effect of illuminance; F = 1.01; p = 0.41; **Fig. 3F**) and yet, they were
232 significantly associated with the activity of the posterior hypothalamus subpart across
233 each illuminance (GLMM; main effect of subpart activity; F = 4.34; **p = 0.04**; **Fig. 3G**). The
234 association was positive meaning that reaction times were longer if activity estimates
235 were higher, which could indicate a reinforcement of the emotional response
236 characterized by longer reactions.[7] No such significant association was detected when
237 considering reaction times to the neutral items of the task (GLMM controlling for age, sex
238 and BMI; main effect of illuminance; F = 1.5; p = 0.21; main effect of subpart activity; F =

0.28; p = 0.6; **Fig. 3H**).

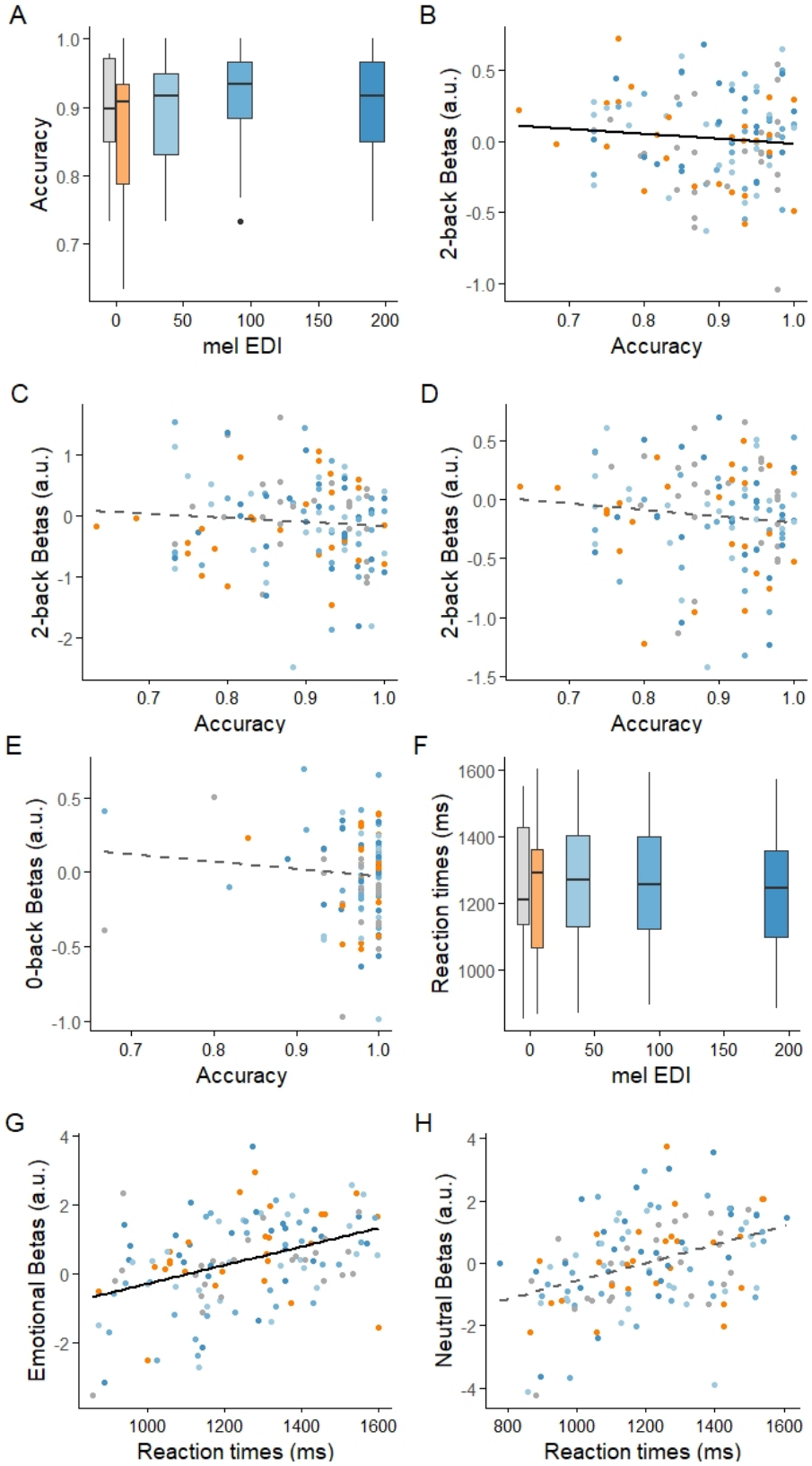

Figure 3. Impact of illuminance on performance and relationships with the activity of the posterior hypothalamus subpart.

(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 S7 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.[1–4] 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.[2,4] We find that the activity of the posterior part of the hypothalamus increases with increasing illuminance while, in contrast, the inferior and anterior hypothalamus show a seemingly opposite pattern and see their activity decrease under higher illuminance. Importantly, performance to the complex cognitive task was improved under higher illuminance and was correlated to the activity

291 of the posterior part of the hypothalamus under the different illuminance, though
292 negatively. The results demonstrate that the human hypothalamus does not respond
293 uniformly to variations in illuminance while engaged in a cognitive challenge, and suggest
294 that the posterior part of the hypothalamus may be key in mediating the stimulating
295 impact of light on cognition.

296 The different nuclei of the hypothalamus do not have clear contrast boundaries
297 based on MRI signals.[8] As a result, achieving nucleus resolution over the human
298 hypothalamus even using UFH MRI remains out of reach.[9] Therefore, we cannot assign
299 the effects we report to a specific nucleus. We can only speculate and present a selection
300 of plausible scenarios that would need to be tested. The posterior part of the
301 hypothalamus - delineated in each participant based on an automatic reproducible
302 procedure[8] - encompasses the MB as well as parts of the LH and the TMN. All these nuclei
303 could participate to the increased BOLD signal we detect under higher illuminance. The
304 LH and TMN, respectively, produce orexin and histamine, which are both known to
305 promote wakefulness, while animal histology reports direct projection of the ipRGCs to
306 the LH.[2–4] Orexin is a good candidate to constitute the circadian signal that promotes
307 wakefulness and to counter the progressive increase in sleep needs with prolonged
308 wakefulness.[10] Our data may therefore be compatible with an increase in orexin release
309 by the LH with increasing illuminance. This would stimulate cognition and maintain or
310 increase alertness[1] and may also be part of the mechanisms through which daytime light
311 increases the amplitude in circadian variations of several physiological features.[11,12] It

312 could then also be part of the mechanisms through which evening light may disturb
313 subsequent sleep[13] when illuminance is higher than the recommended maximum of 10
314 mel EDI lux for evening light.[14] If the TMN was the hypothalamus nucleus underlying the
315 regional increase in the BOLD signal we report, it could confer a role to histamine in
316 mediating the stimulating impact of light. Of interest, the TMN receives orexin signal from
317 the LH.[15] Alternatively, our findings may suggest a role for the MBs in mediating the
318 impact of light on ongoing cognition, potentially influenced through its innervation by the
319 TMN.[16]

320 Previous research indicated that increasing illuminance reduced the activity of the
321 anterior part of the hypothalamus encompassing the SCN, either following the exposure
322 to light[17] or during the exposure.[18] We extend this finding by showing that the significant
323 decrease in activity extends beyond the inferior anterior hypothalamus and therefore
324 much beyond the SCN. The inferior-tubular and inferior-anterior subparts of the
325 hypothalamus – also isolated based on an automatic reproducible procedure[8] -
326 encompass several nuclei such as notably the SCN, SON, ventromedial nucleus of the
327 hypothalamus, arcuate nucleus and part of the TMN. Again, all these nuclei may be
328 involved in the reduction in BOLD signal we observe at higher illuminance. In terms of
329 chemical communication, these changes in activity could correspond to a modification of
330 the γ-aminobutyric acid (GABA) internal or external signalling of the SCN which has been
331 implicated in its response to light.[19] GABA produced by the SCN has also been reported
332 to have excitatory properties such that the BOLD signal changes we report may

333 correspond to a reduction in excitation.[19] Likewise, the SCN is also producing other
334 neuropeptides that could affect its downstream targets. As the inferior-tubular subpart
335 of the hypothalamus also includes part of the TMN it may be the TMN and its GABA
336 production that is decreased by higher illuminance.[15] The decrease in BOLD signal with
337 increasing illuminance we report could therefore arguably reflect a decreased inhibitory
338 signal arising from the anterior and inferior nuclei of the hypothalamus.

339 Importantly, none of the scenarios we elaborated on are mutually exclusive and
340 we stress overlooked the potential implication of several nuclei as well as the cellular
341 diversity of the nuclei of the hypothalamus.[3,20] We further note that the anterior-superior
342 hypothalamus subpart of the hypothalamus encompassing the VLPO and PON sees its
343 activity decreasing under higher illuminance during the emotional task, similarly to the
344 anterior-inferior and inferior-tubular areas. Likewise, similar to the posterior subpart, the
345 activity of the superior-tubular hypothalamus subpart may be increased under higher
346 illuminance during the emotional task. Whether this represents a task-specific effect
347 arising, for instance, from differences in the salience of the auditory stimulus, remains to
348 be determined.

349 A critical aspect of our results is that the performance to the 2-back (executive)
350 subtask was significantly increased when exposed to higher illuminance light. The extent
351 of this increase was limited, likely because performance was overall high at all
352 illuminances, but was not detected for the simpler detection letter subtask (0-back). The
353 result contrasts with many previous 3T MRI investigations on the biological effects of light

354 on human brain function which did not report behavioural changes induced by repeated
355 short exposures to light (e.g. [21–23] but see [24,25]). Our 7T MRI study, which includes a sample
356 size larger than many of these previous studies, supports that BOLD fMRI is sensitive in
357 detecting subtle impacts of light on the brain and that these detected changes can
358 arguably contribute to the behavioural changes others reported using longer light
359 exposure and other approaches (e.g. [26,27] but see [28]).

360 Importantly, we find that activity of the posterior hypothalamus subpart is
361 negatively related to the performance to the executive task, making it unlikely that it
362 mediates directly the positive impact of light on performance. The activity of the posterior
363 hypothalamus was, however, associated with an increased behavioural response to the
364 emotional stimuli. The association between behaviour and the posterior hypothalamus is
365 therefore likely to be complex and may depend on the context, with for instance different
366 nuclei or neuronal populations contributing in some instances but not in others.[15,20] It is
367 likely also to work jointly with the decreased activity of the anterior/inferior
368 hypothalamus we detected as well as with other non-hypothalamus subcortical
369 structures regulating wakefulness to influence behaviour, which intrinsically primarily
370 depends on cortical activity. Future research should assess the impact of light on other
371 subcortical structures and on entire subcortical network to determine how illuminance
372 modifies their crosstalk as well as their interaction with the cortex, to eventually lead to
373 behavioural impacts. These analyses could for instance address whether the regional
374 changes in activity of the hypothalamus we find are upstream of the repeatedly reported

375 impact of light illuminance on the activity of the pulvinar in the thalamus.[1,24] Although it
376 does not receive direct dense input from ipRGCs, it is likely to indirectly mediate the
377 biological impact of light on ongoing cognitive activity.[29]

378 These knowledge gaps are important to address because acting on light stands as
379 a promising means to reduce high sleepiness and improve cognitive deficits during
380 wakefulness as well as to facilitate sleep in the few hours preceding bedtime.[14,30–35] Light
381 therapy is also a validated means to improve mood and treat mood disorders.[36,37] Light
382 administration can also be considered a simple means to disturb the brain circuitry
383 regulating sleep and wakefulness such that it can provide insights about novel means to
384 improve their quality. For instance, if orexin and histamine were part of the mechanism
385 through which natural light affects brain functions, their administration may be the most
386 ecological and/or natural means to affect alertness and cognition. Likewise, as both orexin
387 and histamine are targets for the treatment of brain disorders, our findings could suggest
388 that light may constitute a non-pharmacological complementary intervention to
389 compounds that are being developed to treat arousal, sleep, or cognitive dysfunction in
390 brain disorders.[38] It remains, however, premature in our view to base recommendations
391 on the therapeutic use of light based on the MRI findings gathered to date. Targeted
392 lighting for interventions or for precise interference of subcortical circuits will require a
393 full understanding of how light affects the brain, particularly at the subcortical level. Our
394 findings represent an important step towards this goal, at the level of the hypothalamus.
395

396 **Methods**

397 The data used in this paper arise from a large study that is leading to several publications
398 and part of the methods have been published previously.[29,39,40] The protocol was
399 approved by the Ethics Committee of the Faculty of Medicine at the University of Liège.
400 Participants gave their written informed consent to take part in the study and received
401 monetary compensation for their participation.

402 **Participants.** Thirty healthy young adults (19 women; 24.3 ± 2.9 y; **Suppl. Table S1**) were
403 included in the analyses. Exclusion criteria were assessed through questionnaires and a
404 semi-structured interview: history of psychiatric and neurological disorders, sleep
405 disorders, use of psychoactive drugs or addiction; history of ophthalmic disorders or
406 auditory impairments; colour blindness; night shift work during the last year or recent
407 trans-meridian travel during the last 2 months; excessive caffeine (>4 caffeine units/day)
408 or alcohol consumption (>14 alcohol units/week); medication affecting the central
409 nervous system; smoking; pregnancy or breast-feeding (women); counter indication for
410 MRI-scanning. All participants had to score < 18 on the 21-item Beck Anxiety Inventory
411 (up to mild anxiety),[41] and on the Beck Depression Inventory-II (up to mild depression),[42]
412 < 12 on the Epworth Sleepiness Scale,[43] and < 8 on the Pittsburgh Sleep Quality Index.[44]
413 Questionnaires further assessed chronotype with the Horne-Östberg questionnaire[45] and
414 seasonality with the Seasonal Pattern Assessment Questionnaire,[46] but the latter two
415 questionnaires were not used for the inclusion of the participants.

416 For each task, 4 datasets were missing or corrupted data such that 26 participants were

417 included in the analyses of each task (23 participants had valid datasets for both tasks).
418 For the emotional task, two participants' data failed the MRI quality control (QC) check,
419 and the other two participants were excluded as they did not complete the entire task.
420 For the executive task, four of the participants' data failed the MRI QC check.
421 **Supplementary Table S1** summarises participants' characteristics respective to each task.
422 **Overall Protocol.** Participants completed an MRI session at least one week before the
423 experiment during which structural images of the brain were acquired and which served
424 as habituation to the experimental conditions. Participants then maintained a loose sleep-
425 wake schedule (± 1h from the habitual sleep/wake-up time) during the 7 days preceding
426 the fMRI experiment to warrant similar circadian entrainment across participants and
427 avoid excessive sleep loss while maintaining realistic real-life conditions (verified using
428 sleep diaries and wrist actigraphy - AX3 accelerometer, Axivity, United Kingdom).
429 Volunteers were requested to refrain from all caffeine and alcohol-containing beverages,
430 and extreme physical activity for 3 days before participating in the fMRI acquisitions. Data
431 acquisitions took place in Liège, Belgium, between December 2020 and May 2023.
432 Participants arrived at the laboratory 1.5 to 2h after habitual wake time for the fMRI scan.
433 They were first exposed for 5 min to a bright polychromatic white light (1000 lux) and
434 then maintained in dim light (< 10 lux) for 45 min to standardise the participant's recent
435 light history. During this period participants were given instructions about the fMRI
436 cognitive tasks and completed practice tasks on a luminance-controlled laptop (< 10 lux).
437 The fMRI session consisted of participants completing three auditory cognitive tasks while

438 alternatively maintained in darkness or exposed to light: an executive task (25 min), an
439 emotional task (20 min) and an attentional task (15 min) [**Fig. 1**]. The executive task was
440 always completed first, as it was the most demanding task. The order of the following two
441 tasks was counterbalanced. Because it included only 3 light conditions (see below) instead
442 of 5 for the other two tasks, the attentional task was not included in the present analyses.
443 An eye-tracking system (EyeLink 1000Plus, SR Research, Ottawa, Canada) was monitored
444 for proper eye opening during all data acquisitions.

445 **Light exposure.** An 8-m long MRI-compatible optic fibre (1-inch diameter, Setra Systems,
446 MA, USA) transmitted light from a light box (SugarCUBE, Ushio America, CA, USA) to the
447 dual end of the fibre which was attached to a stand fitted at the back of the MRI coil that
448 allowed reproducible fixation and orientation of the optic fibre ends. The dual branches
449 illuminated the inner walls of the head coil to ensure relatively uniform and indirect
450 illumination of participants' eyes. A filter wheel (Spectral Products, AB300, NM, USA) and
451 optical fibre filters (monochromatic narrowband orange filter - 589mn; full width at half
452 maximum: 10 nm - or a UV highpass filter - 433–1650nm) were used to create the light
453 conditions needed for the experiment (see **Fig. 1B** and **Suppl. Table S2** for in-detail light
454 characteristics).

455 For the executive and emotional task, the light conditions consisted of three different
456 illuminance of a white, blue-enriched polychromatic LED light (37, 92, 190 mel EDI lux;
457 6500K) and one illuminance level of monochromatic orange light (.16 mel EDI lux; 590nm
458 full width at half maximum - FWHM: 10 nm). For the present analyses, we discarded

459 colour differences between the light conditions and only considered illuminance as
460 indexed by mel EDI lux, constituting a limitation of our study. In the executive task,
461 participants were exposed to 30s to 70s (median 30s) of light blocks separated by 10s of
462 darkness (< 0.1 lux) and the light blocks were repeated 11 times for each light condition.
463 For the emotional task, participants were exposed to 30 to 40s (median 35s) light blocks
464 separated by 20s of darkness (< 0.1 lux) and the light blocks were repeated five times for
465 each light condition.
466 The attentional task only included a single illuminance level of the blue-enriched
467 polychromatic LED light (92 mel EDI lux) and one illuminance level of the monochromatic
468 orange light (.16 mel EDI lux), otherwise the task would have been too long (> 30 min).
469 Participants were exposed to 30s of light blocks separated by 10s of darkness (<0.1 lux).
470 The light blocks were repeated 7 times for each light condition. As mentioned above it is
471 not considered for the present analyses.
472 **Auditory cognitive tasks.** The tasks were programmed with Opensesame (3.2.8).[47]
473 Participants heard the auditory stimuli through MR-compatible earbuds (Sensimetrics,
474 Malden, MA). Before starting the tasks, to ensure optimal auditory perception of task
475 stimuli, participants set the volume through a volume check procedure. Participants used
476 an MRI-compatible keypad to respond to task items (Current Designs, Philadelphia, PA),
477 which was placed in the participant's dominant hand. The tasks were separated by about
478 5 minutes in near darkness, to recalibrate the eye tracking system and to clarify
479 instructions about the next task to the participant.

480 ***Executive Task.*** The task consisted of an auditory variant of the n-back task[6] with a
481 working memory 2-back task and a control letter detection 0-back task. Participants were
482 either asked to detect whether the current item was identical to the letter presented 2
483 items earlier (2-back) or whether the current item consisted of the letter "K" (0-back) or
484 using the keypad (one button for "yes", one button for "no"). A block design was used
485 for this task in which each block included 15 items and lasted 30s. Task blocks were
486 separated by 10-20s rest periods and were preceded by an auditory instruction (500 ms)
487 indicating the type of task to be completed. Task levels were pseudo-randomised across
488 the 4 light conditions with 3 blocks of 0-back and 4 blocks of 2-back per light condition.
489 ***Emotional Task.*** The task consisted of gender discrimination of auditory vocalizations that
490 were either pronounced with emotional or neutral prosody.[7] Participants were asked to
491 use the keypad to indicate what they believed the gender of the person pronouncing each
492 token was. The gender classification was a lure task ensuring participants paid attention
493 to the auditory stimulation. The purpose of the task was to trigger an emotional response
494 as participants were not told that part of the stimuli was pronounced with angry
495 prosodies. The 240 auditory stimuli were pronounced by professional actors (50%
496 women) and consisted of three meaningless words ("*goster*", "*niuvenci*", "*figotleich*").
497 The stimuli were expressed in either an angry or neutral prosody, which has been
498 validated by behavioural assessments[48]Click or tap here to enter text. and in previous
499 experiments.[7,49,50] The stimuli were also matched for the duration (750 ms) and mean
500 acoustic energy to avoid loudness effects. During each 30 to 40-s light block, four angry

501 prosody stimuli and four neutral prosody stimuli were presented in a pseudorandom
502 order and delivered every 3 to 5 seconds. A total of 160 distinct voice stimuli (50% angry;
503 50% neutral) were distributed across the four light conditions. The darkness period
504 separating each light block contained two angry and two neutral stimuli. A total of 80
505 distinct voice stimuli (50% angry; 50% neutral) were distributed across the darkness
506 periods.

507 **Data acquisition**

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

513 Multislice T2*-weighted fMRI images were obtained with a multi-band Gradient-Recalled
514 Echo - Echo-Planar Imaging (GRE-EPI) sequence using axial slice orientation (TR = 2340
515 ms, TE = 24 ms, FA = 90°, no interslice gap, in-plane FoV = 224 mm × 224 mm, matrix size
516 = 160 × 160 × 86, voxel size = 1.4 × 1.4 × 1.4 mm^3). To avoid saturation effects, the first
517 three scans were discarded. To correct for physiological noise in the fMRI data the
518 participants' pulse and respiration movements were recorded using a pulse oximeter and
519 a breathing belt (Siemens Healthineers, Erlangen, Germany). Following the fMRI
520 acquisition a 2D GRE field mapping sequence to assess B0 magnetic field inhomogeneities
521 with the following parameters: TR = 5.2 ms, TEs = 2.26 ms and 3.28 ms, FA = 15°,

522 bandwidth = 737 Hz/pixel, matrix size = 96 × 128, 96 axial slices, voxel size = (2x2x2) mm^3,
523 acquisition time = 1:38 min, was applied.
524 For the anatomical image, a high-resolution T1-weighted image was acquired using a
525 Magnetization-Prepared with 2 RApid Gradient Echoes (MP2RAGE) sequence: TR = 4300
526 ms, TE = 1.98 ms, FA = 5°/6°, TI = 940ms/2830 ms, bandwidth = 240 Hz, matrix size =
527 256x256, 224 axial slices, acceleration factor = 3, voxel size = (0.75x0.75x0.75) mm^3.
528 **Data processing**
529 For the MP2RAGE images, the background noise was removed using an extension
530 (extension: https://github.com/benoitberanger/mp2rage) of Statistical Parametric
531 Mapping 12 (SPM12; https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) under Matlab
532 R2019 (MathWorks, Natick, Massachusetts).[51] Then the images were reoriented using the
533 'spm_auto_reorient' function
534 (https://github.com/CyclotronResearchCentre/spm_auto_reorient) and corrected for
535 intensity non-uniformity using the bias correction method implemented in the SPM12
536 "unified segmentation" tool.[52] To ensure optimal co-registration, brain extraction was
537 done using SynthStrip[53] in Freesurfer (http://surfer.nmr.mgh.harvard.edu/). The brain-
538 extracted T1-images were used to create a T1-weighted group template using Advanced
539 Normalization Tools (ANTs, http://stnava.github.io/ANTs/) prior to normalization to the
540 Montreal Neurological Institute (MNI) space using ANTs (1mm^3 voxel; MNI 152 template).
541 The hypothalamus of each participant was segmented within 1mm^3 MNI 152 template
542 into 5 subparts - inferior anterior, superior anterior, inferior tubular, superior tubular,

posterior [cf. **Fig. 2a**] using an automatic computational approach.[8]

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

Statistical analyses

The whole-brain univariate analyses consisted of a general linear model (GLM) computed with SPM12. For the executive task, task blocks and light blocks were modelled as block functions. For the emotional task, the auditory stimuli were modelled as stick functions. For both tasks, a high-pass filter with a 256 s cut-off was applied to remove low-frequency drifts. For both tasks, stick or block functions were convolved with the canonical hemodynamic response function. Movement and physiological parameters (cardiac, and respiration), which were computed with the PhysIO Toolbox (Translational Neuromodeling Unit, ETH Zurich, Switzerland), were included as covariates of no interest. [54]

Two separate analyses were completed. In the main analyses, we sought to test whether

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

The output masks of the segmentation procedure we used to extract regression betas associated with each of the hypothalamus subpart using the REX Toolbox (https://web.mit.edu/swg/software.htm).[55] 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 subsequence analyses, we obtained 5 activity estimates per stimulus type and per subpart (50 per individual).

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

585 a relatively unspecific and widespread increase in BOLD signal surrounding the
586 hypothalamus.
587 Statistical analyses of the activity of the hypothalamus subparts were performed in SAS
588 9.4 (SAS Institute, NC, USA). Analyses consisted of Generalised Linear Mixed Models
589 (GLMM) with the subject as a random factor (intercept and slope) and were adjusted for
590 the dependent variable distribution. As the main statistical analysis was completed for
591 each task, the significance threshold was corrected for multiple comparisons and was set
592 at $p < 0.025$. Direct post hoc of the main analyses were corrected for multiple comparisons
593 using a Tukey adjustment. The subsequent more detailed analyses were considered as
594 post hoc that were not corrected for multiple comparisons ($p < 0.05$). To detect outlier
595 values within the data sets, Cook's distance > 1 was used for exclusion. No outliers were
596 detected for activity estimates of both tasks, while four outlier values were removed from
597 the analyses of the 2-back and 0-back performance.
598 The main analyses included the activity estimates modulated by light illuminance as a
599 dependent variable and the hypothalamus subpart and stimulus type (2-back/0-back –
600 neutral/emotional) as repeated measures (autoregressive (1) correlation), together with
601 age, sex and BMI as covariates. The second set of post hoc GLMM analyses included the
602 activity estimates of the hypothalamus subparts as the dependent variable and
603 hypothalamus subpart, stimulus type and illuminance (0, 0.16, 37, 92, 190 mel EDI lux) as
604 the repeated measures (autoregressive (1) correlation), together with age, sex, and BMI
605 as covariates and interaction term between illuminance and hypothalamus subpart. The

606 final set of analyses included performance metrics as dependent variables (accuracy to
607 the 2-back or 0-back task - as percentage of correct responses; reaction time – ms - to
608 emotional or neutral stimuli during the emotional task) and included the same repeated
609 measures and covariates ads in the preceding set as well as activity of the relevant
610 hypothalamus subpart.

611 Optimal sensitivity and power analyses in GLMMs remain under investigation (e.g. [56]). We
612 nevertheless computed a prior sensitivity analysis to get an indication of the minimum
613 detectable effect size in our main analyses given our sample size. According to G*Power
614 3 (version 3.1.9.4),[57] taking into account a power of 0.8, an error rate α of 0.025
615 (correcting for 2 tasks), and a sample of 26 allowed us to detect large effect sizes $r > 0.54$
616 (two-sided; absolute values; CI: 0.19–0.77; $R^2 > 0.29$, R^2 CI: 0.04–0.59) within a multiple
617 linear regression framework including one tested predictor (illuminance effect) and three
618 covariates (age, sex and BMI).

619

620 **Data and code availability statement**

621 The processed data and analysis scripts supporting the results included in this manuscript
622 are publicly available via the following open repository:
623 https://gitlab.uliege.be/CyclotronResearchCentre/Public/xxxx (the repository will be
624 created following acceptance / prior to publication of the paper).

625

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Tables

Table 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**	**$P_{uncorrected}$**	**$P_{corrected}$**
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**	**$P_{uncorrected}$**	**$P_{corrected}$**
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	0.053		1 vs. 5	-2.24	**0.025**	0.17
Hypothalamus subparts x stimulus type	0.55	0.7		2 vs. 3	-5.09	**< 0.0001**	**0.0001**
				2 vs. 4	-0.37	0.71	0.99
				2 vs. 5	-2.57	**0.011**	0.081
Age	0.18	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

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

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

refer to Figure 2A for correspondence of subpart numbers

Table 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 R²**	**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 R²**	**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					

* illuminance in mel EDI lux

only significant comparisons are reported in the main text. For the full table, including post hocs comparing light levels within a subpart, refer to Suppl. Table S3 to S6