Exposure to light supresses the activity of the medial and superior amygdala during emotional processing

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

Short Title: Light modulates the amygdala during emotional processing

[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.

***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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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 and code 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 of the paper / upon request of the editor).

Abstract

Background: Light can influence several non-image-forming biological effects including the modulation of mood and emotional processing through neural circuitry that remains to be fully established. Rodent data showed that nuclei the amygdala, known to be important to mood regulation and emotional processing, receive direct inputs from the retina and mediate part of the affective impact of light. Here, we wanted to assess whether these animal findings translate to human beings. We determine the dynamics of the impact of light exposure on the activity of the amygdala, and whether the dynamics varied across its volume, during the processing of emotional stimulation.

Methods: We used 7 Tesla functional magnetic resonance imaging to assess the impact of variations in light illuminance on the regional activity of the amygdala in healthy young adults (N = 29; 18 women; 24 ± 3.1y) during an auditory emotional task.

Results: We find that several subregions of the amygdala, including the medial nucleus that receives direct retinal projection, showed a marked and linear reduction of activity with increasing illuminance when processing emotionally charged stimuli.

Conclusion: We speculate that it is through the medial nucleus that light affects the emotional state of healthy individuals. These findings shed more light on the mechanisms that underlie the biological impact of light on the brain and may contribute to the benefits of light therapy in the treatment of mood disorders.

56 Introduction

57

58 Bright light therapy is established as a non-pharmacological treatment for seasonal affective
59 disorder (SAD) and is also considered an efficient adjunct therapy for other non-seasonal psychiatric
60 disorders (1,2). Previous research reported that the mechanisms of action of light on human mood
61 could involve the production of serotonin and dopamine (3–5), the normalisation of rods and cones
62 functioning in the retina (6), the improvement of circadian entrainment (3,6), or an impact on the
63 brain emotional processing (7,8). Light's influence on mood in humans may be mediated through a
64 light-sensitive pathway of the retina (9,10) that detects environmental irradiance and is often
65 referred to as the non-image forming (NIF) pathway (11). The NIF system mostly mediates light
66 influence on functions not directly related to image formation, including melatonin suppression (12),
67 stimulation of alertness and cognitive performance (13) and circadian entrainment (14). Intrinsically
68 photosensitive retinal ganglion cells (ipRGCs) are the main photoreceptors of the NIF system. They
69 express the photopigment melanopsin, which is maximally sensitive to blue-wavelength light
70 (~480nm) (15), and combine their intrinsic photosensitivity to inputs from rods and cones (16) to
71 influence multiple brain targets with a maximal efficiency shifted toward blue wavelengths (17).

72 Interestingly, many of these brain targets are involved in mood regulation and emotional processing
73 (15). The perihabenular zone, ventral lateral geniculate nucleus and intergeniculate leaflet, all
74 receive ipRGCs innervation and have been implicated in pathways mediating light's influence on
75 depressive-like behaviours in animal models (18,19). Rodent data also showed that the amygdala
76 also received direct inputs from ipRGCs (15,20). The amygdala is a complex structure that is divided
77 into 13 nuclei, though their exact classification is still debated (21). In rodents, ipRGCs project to the
78 central nucleus of the amygdala (CeA) and the pathway was found to mediate anxiety-related
79 behaviour after acute light exposure (22,23). Lesions of the medial amygdala, to which ipRCGs also
80 project, induced altered light-enhanced startle and open-field behaviour, suggesting that the effects
81 of light on anxiety may also be mediated by the ipRGCs innervation of the medial amygdala (24).

Given the known involvement of the amygdala in psychiatric disorders (25–27), knowing which of its nuclei respond to light may provide a basis to extend the use of light treatment to novel brain disorders.

In vivo, functional Magnetic Resonance Imaging (fMRI) in humans suggested that blue-wavelength light enhanced the responses to emotional stimuli in the amygdala as well as its crosstalk with the hypothalamus (7). In contrast, another resting-state fMRI study found that exposure to a warm polychromatic white light suppressed amygdala activity and connectivity between the amygdala and the ventromedial prefrontal cortex during light exposure (28). The discrepancies may arise from differences in the light sources or from being engaged in a cognitive task vs. at rest. They may also be due to the context-dependent response of the different nuclei of the amygdala that could not be addressed given the data resolution.

Here we aimed to determine the dynamics of the impact of light exposure on the activity of the amygdala, and whether the dynamics varied across its volume, during the processing of emotional stimuli. We took advantage of the relatively high resolution of ultra-high-field (UHF) 7 Tesla (7T) fMRI to record the activity of the amygdala in healthy young adults exposed to the light of various illuminance while engaged in an auditory emotional task. The findings reveal that the medial part of the amygdala shows a marked reduction of activity under higher illuminance when processing emotionally charged stimuli. The finding sheds more light on the mechanisms that may underlie the benefits of light therapy.

Methods and Materials

This paper arises from a larger study and part of the methods have been described previously (29–32). The protocol was approved by the Ethics Committee of the Faculty of Medicine at the University of Liège. Participants gave their written informed consent and received monetary compensation. Data acquisitions took place in Liège, Belgium, between December 2020 and May 2023. Additional methodological details are provided as supplementary methods.

Protocol

Thirty-six healthy participants (23.9y±2.8; 23 women) took part in the study. Seven datasets were missing or corrupted such that 29 participants (24y±3.1; 18 women; **Supplementary Table 1**) were included in the present analyses (four failed quality control checks; three incomplete task completion).

Participants followed a loose sleep-wake schedule (±1h from habitual sleep/wake-up time) for 7 days (verified using wrist actigraphy -AX3, Axivity, UK- and sleep diaries) and then arrived at the laboratory 1.5 to 2h after their habitual wake time. To standardise participants' light history, they were exposed to 5min of bright white light (1000 lux) and were then maintained in dim light (<10 lux) for 45min. The fMRI sessions consisted of an executive task (25min), an attentional task (15min), and an emotional task (20min) [**Fig.1A**]. Only the emotional task is discussed in the present paper.

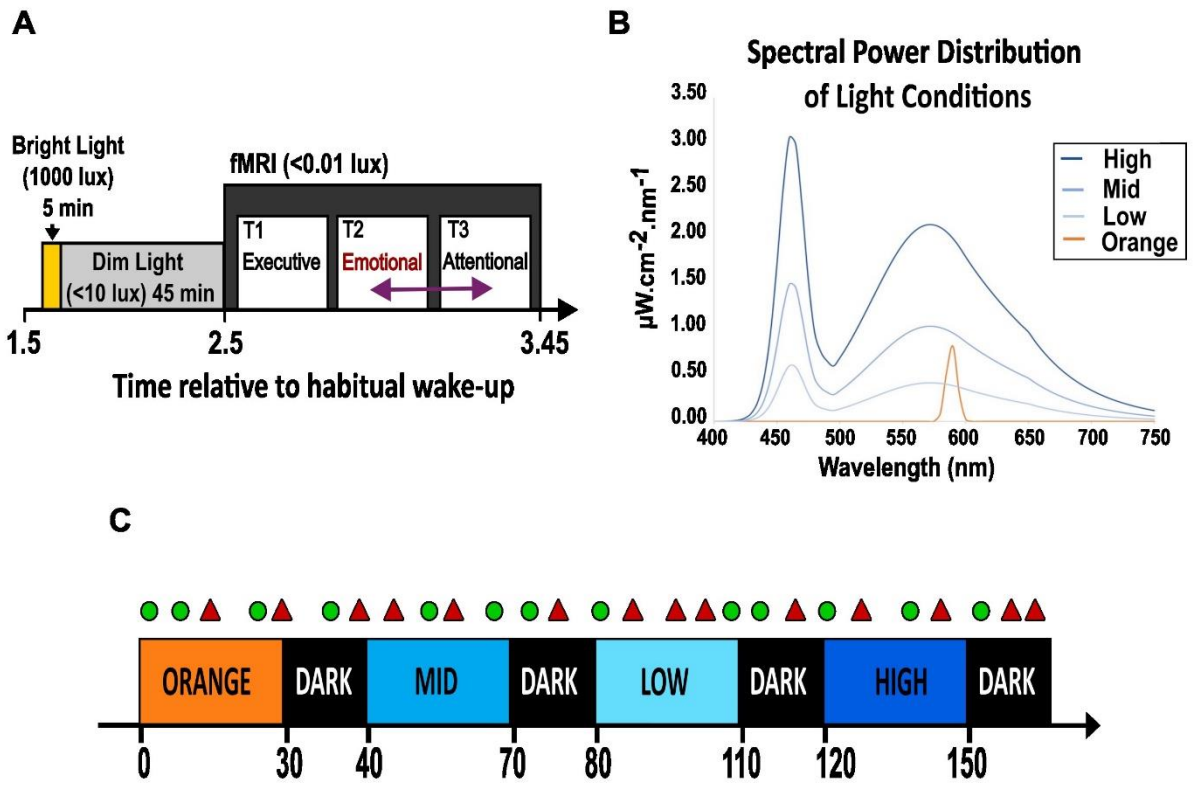

Figure 1. Experimental protocol

(A) Overall timeline. After prior light history standardisation, participants performed an executive (always first), an emotional and an attentional task (pseudo-randomly 2nd or 3rd, purple arrow). Only the emotional task is considered in the present manuscript. **(B) Spectral power distribution of light exposures**. Monochromatic orange: 0.16 mel EDI lux; Polychromatic, blue-enriched light (6500K); LOW, MID, HIGH: 37, 92, 190 mel EDI lux (**Supplementary Table S2** for full details). 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 (7, 8). The orange light was introduced as a control visual stimulation for potential secondary whole-brain analyses. For the present region of interest analyses, we discarded colour differences between the light conditions and only considered illuminance as indexed by mel EDI lux, constituting a limitation of our study. **(C) Tasks procedures**. Time is reported in seconds relative to session onset; participants were pseudo-randomly exposed to the four light conditions. Emotional task: lure gender discrimination of vocalizations (50% angry (red triangle), 50% neutral (green circle).

Light Exposure

An MRI-compatible system was developed to ensure relatively uniform and indirect illumination of participants' eyes whilst in the scanner. Participants were exposed to 30 to 40s blocks of light (median 35s) separated by 20s of darkness (<0.1 lux). The light conditions used were three different illuminance of a blue-enriched white LED light (37, 92, 190 melanopic equivalent daylight

139 illuminance (mel EDI) lux) and a monochromatic orange light (0.16 mel EDI lux) [**Fig.2B**]. For the
140 present analyses, we discarded colour differences between the light conditions and only considered
141 illuminance. The light blocks were repeated five times per light condition.

142 Emotional Task

143 The task consisted of gender discrimination of auditory vocalizations (33) [**Fig. 2C**]. Participants were
144 asked to use a keypad to indicate what they believed the gender of the person pronouncing each
145 token was. The gender classification was a lure task: its purpose was to trigger an emotional
146 response as participants were not told that 50% of the stimuli were pronounced with angry
147 prosodies. The 240 auditory stimuli were pronounced by professional actors (50% women) and
148 consisted of three meaningless words ("*goster*", "*niuvenci*", "*figotleich*"). The stimuli were expressed
149 in either an angry or neutral prosody (validated by behavioural assessments (33) and in previous
150 experiments (34,35)). A total of 160 distinct voice stimuli (50% angry; 50% neutral) were distributed
151 across the four light conditions. The darkness periods separating light blocks contained two angry
152 and two neutral stimuli (80 stimuli in total).

153 Data acquisition

154 MRI data were acquired in a 7T MAGNETOM Terra MR (Siemens Healthineers, Erlangen, Germany)
155 with a 32-channel receive and 1-channel transmit head coil (Nova Medical, Wilmington, MA, USA).
156 Multislice T2*-weighted fMRI images were obtained with a multi-band Gradient-Recalled Echo -
157 Echo-Planar Imaging (GRE-EPI) sequence (TR=2340ms, voxel size: (1.4×1.4×1.4)mm^3). The anatomical
158 image consisted of a T1-weighted image Magnetization-Prepared with 2 RApid Gradient Echoes
159 (MP2RAGE) sequence (voxel size: (0.75x0.75x0.75)mm^3)

160 Data analysis

161 The brain-extracted anatomical T1-images were used to create a T1-weighted group template using
162 Advanced Normalization Tools (ANTs, http://stnava.github.io/ANTs/) before normalization to the

163 Montreal Neurological Institute (MNI) space using ANTs (1mm³ voxel; MNI 152 template). For each
164 subject, the first level analysis of fMRI data was performed in the native space. Before the group
165 analysis, statistical maps were first transferred to the group template space and then the MNI space
166 (1x1x1mm^3 resolution; MNI 152 template) using ANTs.

167 Our statistical analyses consisted of an a priori region of interest focused on the activity of the
168 amygdala which was estimated as part of a whole brain general linear mixed model computed with
169 SPM12. The auditory stimuli were modelled as stick functions convolved with a canonical
170 hemodynamic response function. There were two parts to the whole-brain analysis. In the main
171 analysis, we assessed how brain responses during the task were modulated by overall changes in
172 illuminance level. The two regressors of task events (neutral, angry) were each accompanied by a
173 parametric modulation corresponding to the light melanopic illuminance level (0, .16, 37, 92, 190
174 mel EDI). The contrasts of interest consisted of the main effect of the parametric modulations. In the
175 next whole-brain analysis, we assessed the responses to the stimuli under each light condition.
176 Separate regressors modelled each task's event type under each light condition. The contrasts of
177 interest consisted of the main effects of each regressor. Whole-brain group results over the entire
178 sample were used for visualization purposes only.

179 We used an amygdala atlas to segment the region into 10 subparts (bihemispheric) in the MNI
180 subject space (36), corresponding to nuclei or nucleus groups (**Fig 2.A**). The REX Toolbox
181 (https://web.mit.edu/swg/software.htm) was used to extract the activity estimates (betas) from
182 contrast of interest in each amygdala subpart (37). In the first analysis, this yielded 1 activity
183 estimate per stimulus type and per amygdala subpart and in the second analysis we obtained 5
184 activity estimates per stimulus and subpart.

185 Statistical analyses of the activity of each subparts were computed in SAS 9.4 (SAS Institute, NC, USA)
186 and consisted of Generalised Linear Mixed Models (GLMM) with the subject as a random factor
187 (intercept and slope) and were adjusted for the dependent variable distribution. As main the

statistical analysis included all subparts, light conditions and stimulus types in a single model, the significance threshold was not corrected for multiple comparisons and was set at $p < 0.05$. Direct post hoc of the main analyses were corrected for multiple comparisons using a Tukey adjustment. Activity estimates were considered outliers if > ±3 SDs across emotional stimuli and light level and were removed.

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

Results

Participants achieved 92±7.3% (mean ±SD) button response, while the accuracy to the lure gender classification task (34) was 79.7%±9.9%, which is slightly lower than previous studies using the same task (35). Critically, the reaction times were faster for the neutral (1203±183ms) as compared with the emotional stimuli (1249±184ms) (main effect of stimulus type; p=0.0009). This is in line with previous literature (7,35) and confirms that the emotional content of the stimuli was successful in triggering a behavioural response [**Fig. 2C**]. The reaction times to the neutral or emotional stimuli were not significantly affected by illuminance (neutral: p = 0.3; emotional: p=0.6). This does not, in principle, preclude light from affecting brain activity and ensures that modifications in brain activity are not merely the results of a change in reaction times.

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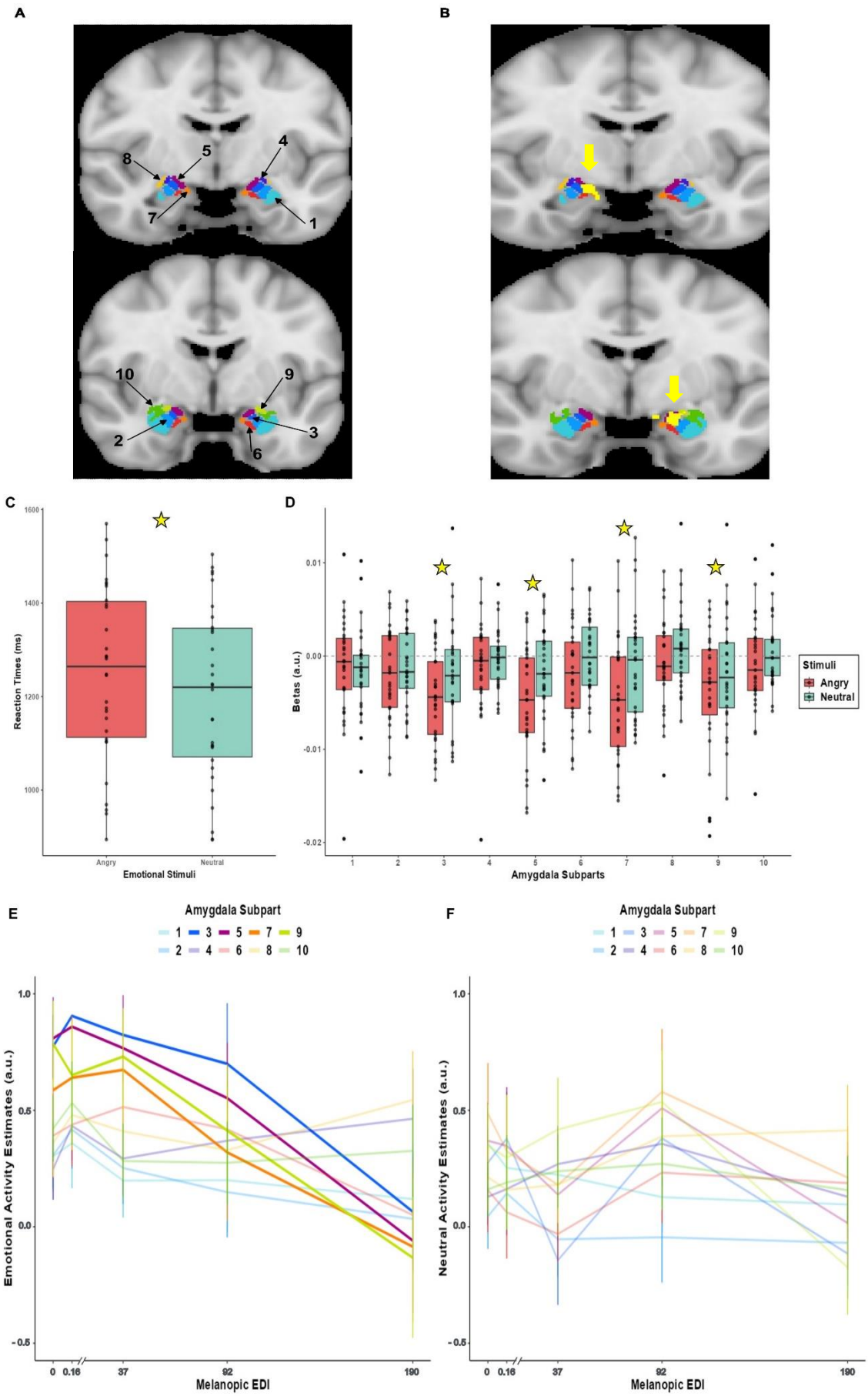
A
B
C
D
E
F
Reaction Times (ms)
Emotional Stimuli
Angry
Neutral
Betas (a.u.)
Amygdala Subparts
Stimuli
Angry
Neutral
Amygdala Subpart
Emotional Activity Estimates (a.u.)
Neutral Activity Estimates (a.u.)
Melanopic EDI

Figure 2. Illuminance impact on the amygdala subparts.

(A) Segmentation of the amygdala into ten subparts. The amygdala template isolate nuclei and nucleus groups as follows: (1) Lateral nucleus, (2) Intermediate and dorsal basolateral nucleus, (3) Basomedial nuclei, (4) Central nucleus, (5) Medial and Cortical nuclei, (6) Ventral basolateral nucleus and Paralaminar nucleus, (7) amygdala transition area composed of Amygdalocortical area, Amygdalohippocampal area, Periamygdaloid cortex, (8) Amygdalostriatal, (9) Anterior amygdaloid area, (10) Intercalated nuclei (36).
(B) Visualization of the whole brain results over the entire sample. Visualization of the whole brain analyses of the collective impact of the emotional variations in illuminance over the amygdala area. A local negative peak (yellow arrow and yellow cluster; $p_{uncorrected}$<.001) was detected bilaterally in the amygdala mostly over the subparts 3, 5 and 7 in the left hemisphere and over subparts 3, 5 and 9 in the right hemisphere. These results indicate that our finding does not arise from a nearby "leaking" deactivation.
(C) Reaction times to neutral and angry stimuli (p=.0009).
(D) Estimates (beta; arbitrary unit – a.u.) of the collective impact of illuminance variation on the activity of each amygdala subpart. Significant main effect of amygdala subparts (p<.0001), significant main effect of stimulus type (p<.0001) and no subpart-by-stimulus-type interaction (p=.4).
(E-F) Estimates of the impact of each illuminance on the activity of the amygdala subparts. Results are displayed per stimulus type. Amygdala subparts showing significant changes are highlighted in bold. Significant stimulus type-by-illuminance interaction (p=.001) and significant illuminance-by-amygdala interaction detected (p=.04) (Refer to Table 1 & 2 and Suppl. Tables S4-S5 for full statistics).

Impact of illuminance variation on the activity of the amygdala

We used a template that consistently divided the amygdala into 10 subparts (36) (**Fig. 2A-B**) to extract the regional effect of illuminance change across the amygdala. The first analysis focussed on the overall impact of illuminance variation. It revealed that the variations in illuminance affected the activity of the 10 amygdala subparts differently (main effect of subparts; p<.0001) [**Fig. 2D, Table 1**], as well as significant differences between stimulus types (main effect of stimulus type; p<.0001).There was no interaction between the stimulus types and subparts (p=.4). The post hoc analyses found that the basomedial nucleus (subpart 3, dark blue on **Fig. 2A**), medial and cortical nuclei (subpart 5, violet on **Fig. 2A**), amygdala transition areas (ATA) (subpart 7, orange on **Fig. 2A**), and anterior amygdaloid area (AAA) subparts (subpart 9, light green on **Fig. 2A**) were reacting significantly differently to light illuminance compared to other amygdala subparts [**Table 1; Supplementary Table S3**]. Interestingly the medial and cortical subpart was significantly different from the central nucleus subpart. Overall, the results suggest that the medial and superior region of the amygdala - encompassing 4 subparts of our template – reacts differently to illuminance change than the rest of the amygdala and undergoes an overall decrease in activity with increasing

illuminance. This is supported by the visualization of the whole brain group analysis ($p_{uncorrected}$<0.001) which yielded local negative peaks bilaterally in the amygdala, mostly over the left subparts 3, 5 and 7 and the right subparts 3, 5 and 9 (**Fig. 2A**) indicating that our finding does not arise from a nearby "leaking“ deactivation.

Amygdala subparts under each illuminance

Following our main analysis, we investigated in more detail the regional impact of light across the amygdala using the activity estimates of each subpart under each illuminance. As in the main analysis, the analysis confirmed that there was a significant impact of stimulus type (p<.0001) and light level (p<.0001) , while there was no significant main effect of amygdala subparts (p=.1). Critically, on top of a significant interaction between illuminance and task stimuli (p=.001), the analyses yielded an illuminance-by-subpart-interaction confirming that the impact of illuminance significantly varied across subparts (p=.04) [**Fig. 2E-F; Table 2**].

We computed post hoc contrasts and first considered the impact of the changes in illuminance within each amygdala subpart (**Table 4; Supplementary Table S4**). We found that the activity of the four medial/superior subparts isolated in the main analysis (basomedial nucleus (light blue), medial and cortical nuclei (purple), ATA (light green), AAA (orange)) was significantly decreased under the highest illuminance (190 mel EDI) when compared to darkness (0 mel EDI lux) and the lowest illuminance level (.16 mel EDI lux). The activity of three of the four nuclei, i.e. the basomedial nucleus, medial and cortical nuclei, and ATA, were also significantly decreased when compared to blue-enriched light of the lower illuminances (37, 92 mel EDI lux). Importantly, there were no significant differences between the other amygdala subparts. Next, post-hoc examined differences between amygdala subparts under each illuminance (**Supplementary Tables S5)** and found only the AAA subpart (orange) was significantly different from the ATA subpart (light orange) at the highest illuminance level (190 mel EDI lux). There was no significant difference between subparts at any other illuminance levels (**Supplementary. Table S6 and S7** for all post hoc comparisons).

Overall, these analyses indicate that increasing illuminance progressively and relatively linearly decreases the activity of the medial/superior regions of the amygdala specifically for the processing of emotional stimuli while activity was more stable across the rest of the amygdala.

Performance and amygdala activity

In the last step, we assessed whether the activity of one of these 4 subparts was related to performance. We found that the association between the activity of the AAA subpart and the reaction times to the emotional stimuli reached nominal significance (GLMM; main effect of subpart activity; F=3.63; **p=.05**; **Fig. 3A**). The association was negative such that higher activity in the subpart was associated with faster reaction times. No such significant association was detected when considering reaction times to the neutral items (GLMM; main effect of illuminance; F=.93; p=.4; main effect of subpart; F=.03; p=.8; **Fig. 3B**). No significant association was found when considering the activity of the other subparts.

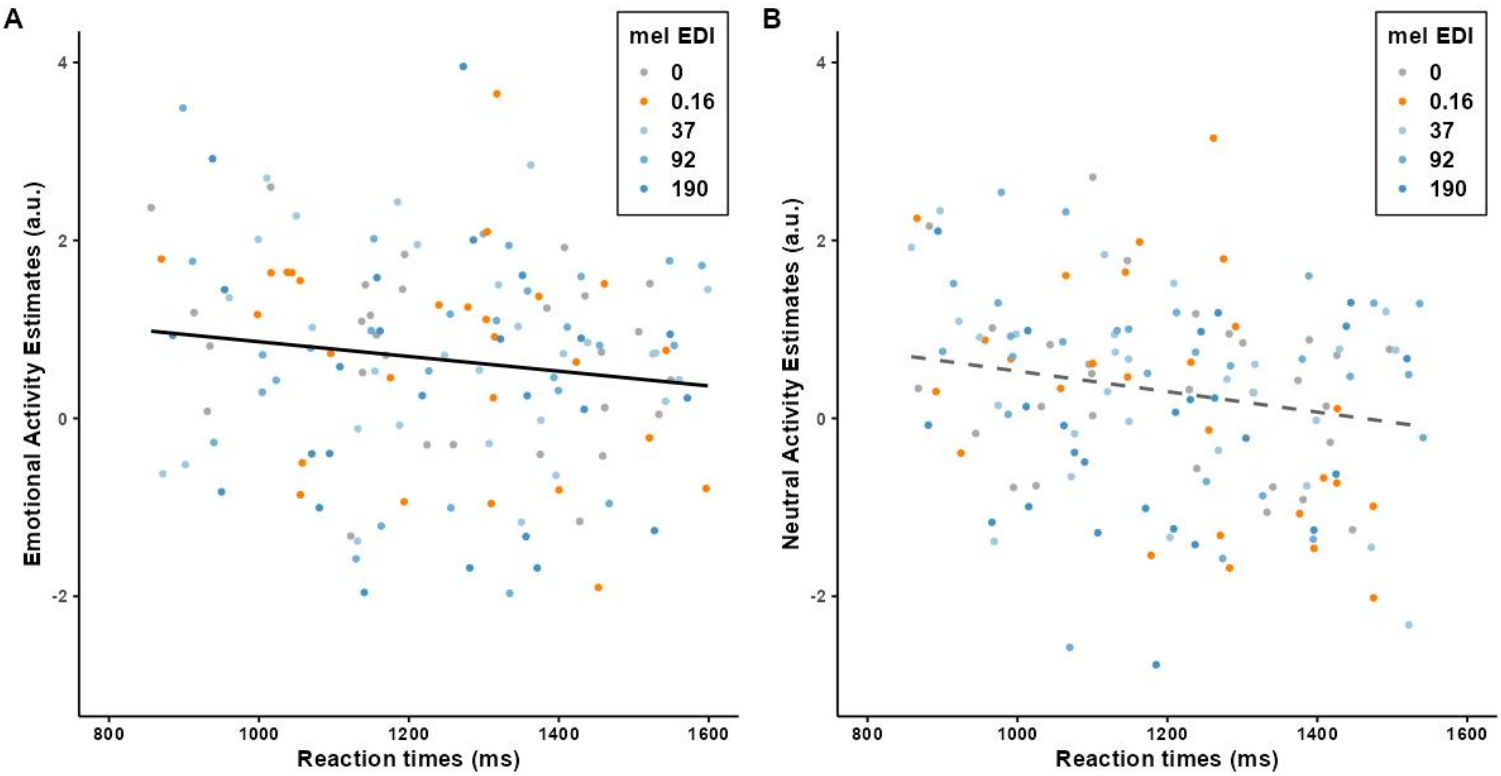

Figure 3. Impact of illuminance on performance and relationships with the activity of the anterior amygdaloid area subpart.

(A) Reaction times to the emotional stimuli are correlated to the activity of the anterior amygdaloid area subpart ($p = 0.05$).

(B) Reaction times to the neutral stimuli are not correlated to the activity of the anterior amygdaloid area subpart ($p = 0.8$).

Solid and dashed lines correspond to the significant and non-significant linear regression lines, respectively.

301 Discussion

302 Light therapy is effective in treating several mood disorders (1,2). The underlying
303 mechanisms have not been fully resolved, however, but it is likely to involve the amygdala
304 (38). Considering the connection between the neural pathways involved in emotional and
305 mood regulation (39), we aimed to determine which subpart of the amygdala was affected
306 by light during the processing of emotional stimulation. We found that the medial and
307 superior region of the amygdala showed a linear reduction of activity with increasing
308 illuminance, specifically when processing emotional stimulations. Furthermore, the activity
309 of part of these regions may be related to the behaviour during the task. These findings
310 provide new insight on the mechanisms that underlie the biological impact of light on the
311 brain and may contribute to the benefits of light therapy in the treatment of mood
312 disorders.

313 Research in rodents reported that the central and medial amygdala receives direct inputs
314 from ipRGCs, and both projections were implicated in the impact of light on anxiety-related
315 behaviours (22–24,40). Neuroimaging research reported that light influences the activity of
316 the amygdala including during emotional processing but did not isolate the nuclei involved
317 (7,28). The template we used to parcellate the amygdala includes 10 subparts (48), one of
318 which corresponding to the central nucleus, one to the basomedial nucleus and a third one
319 to medial and cortical nuclei together, as their boundaries are not well defined enough on
320 MRI images to separate them (36). We found that the basomedial and medial/cortical
321 nucleus subparts show decreased activation with higher illuminances. In contrast, the
322 central nuclei subpart did not show significant variations with illuminance changes. Our
323 results support therefore that in humans it is the medial nucleus rather than the central
324 nucleus that mediates the impact of light on emotional state. This provides support to the

325 existence of a functional projection from ipRGCs to the medial part of the amygdala, similar
326 to rodents (15). This would mean that alike mice, light can influence emotional status
327 independent of the suprachiasmatic nucleus (SCN), which receive the strongest inputs from
328 ipRGCs based on studies in animals and is the site of the principal circadian clock (15,41).
329 Our data are, however, also compatible with an effect of light on the basomedial and medial
330 nucleus activity through the SCN. Future connectivity analyses could help choosing between
331 these alternatives.

332 The basomedial and medial nuclei send reciprocal projections to each other and both
333 project to the cortical nucleus (42). In addition, a simplified overview of sensory information
334 flow through the amygdala is that information enters through the basolateral nuclei and
335 then progresses through to the cortical and medial nuclei which acts as an output station for
336 downstream targets (20). We show therefore that light seems to affect emotional
337 processing at the level of the entry doors of the amygdala.

338 Activation of the medial nucleus is associated with stress and leads to the secretion of
339 adrenocorticotropic hormone and the activation of the hypothalamic–pituitary axis (a
340 neuroendocrine system that maintains physiological homeostasis) (20). The medial nuclei
341 mainly contain GABAergic neurons (43) suggesting that it fulfil its functions mainly through
342 an inhibitory influence on downstream areas, within and outside the amygdala. Based on
343 our finding, one could postulate that light reduces or inhibits this inhibitory influence. The
344 hypothesis that ipRGCs have the potential to be inhibitory is not without evidence, as a
345 rodent study found that a subset of ipRGCs release the inhibitory neurotransmitter GABA at
346 brain targets (SCN, IGL, vLGN), leading to reduced sensitivity of the pupil to light and
347 circadian photoentrainment (44).

348 Aside from the basomedial and medial/cortical subparts, we also find a significant impact of
349 illuminance on the ATA, encompassing amygdalocortical area, amygdalohippocampal area,
350 and periamygdaloid cortex, and AAA. Providing plausible interpretations for their responses
351 is more complicated, as there is less research on these areas. The amygdalohippocampal
352 area, and the periamygdaloid cortex both receive projections from the basomedial and
353 medial nuclei and projects back to the medial nuclei (42). The AAA is less developed in
354 primates and would rather receive projections from the lateral and central nuclei (20,42).
355 Although we do not have empirical data to support this hypothesis, we tentatively speculate
356 that given the high interconnectivity of the amygdala nuclei, the deactivation in the ATA and
357 AAA in response to illuminance change reflects the downstream propagation of signals from
358 output of the basomedial and medial/cortical nuclei. While the visualization of whole brain
359 results over the entire sample supports a local decrease of activity over the area covered by
360 all four nuclei it does not point toward one of them in particular. Ultimately, although we
361 favour an impact of light on the amygdala through the direct projection of the retina to the
362 medial nuclei, all four subparts could equally contribute to the decrease BOLD signal we
363 detect under higher illuminance (42).

364 We stress that the validated auditory emotional task we used (7,34,35) was successful in
365 triggering emotional responses, both at the level of behaviour and of the activity of the
366 amygdala. Behavioural measures (reaction times) were, however, not significant different
367 across the short light exposures of different illuminance. We do find a nominal significant
368 link between reaction time and the activity of the AAA, which is significantly affected by
369 illuminance. It is however unclear how this finding may explain how longer light exposures
370 may affect behaviours both acutely and over the longer term.

371 The processing of negative stimuli has been associated with increased activity in the
372 amygdala whereas positive stimuli have been associated with decreased activity in the
373 amygdala (45). A functional neuroimaging study that focused on bright light therapy in
374 healthy young participants found that after three weeks of light therapy, there was a dose-
375 dependent decrease in the response to emotional stimuli in the amygdala and the medial
376 prefrontal cortex (46). Our finding support that the reduces responsiveness of (part of) the
377 amygdala is already present acutely, during the exposure. The sizes of the effects we
378 detected are small such that light exposure may be beneficial to emotional state through a
379 repeated reduction of the response of the basomedial and medial parts of the amygdala.

380 The amygdala sends a large number of downstream projections including to the frontal
381 cortex, which governs cognition. The basomedial and medial nuclei and the periamygdaloid
382 cortex project to the frontal cortex (42). In addition, one of the main targets of the medial
383 nucleus consist of the hypothalamus, over the anterior paraventricular nucleus, while the
384 basomedial nucleus also projects to the hippocampus and ventral striatum (42,47). Future
385 research will address which of these projections may underlie the impact of light on
386 emotion processing and/or on beneficial impact of light on emotional state.

387 The decrease of activity we find in several subparts of the amygdala contrasts with previous
388 research done using 3T fMRI in healthy participants that found that exposure to light
389 increased the response of the amygdala to emotional stimuli using the same emotional task
390 (7). The conflicting findings may be due to the differences in light sources used as it was a
391 monochromatic blue light (corresponding to illuminance of ~22and 93 mel EDI lux). In
392 contrast, another 3T resting state MRI, which did not involve a cognitive task, found that the
393 activity of the amygdala was decreased under polychromatic white light (~35 mel EDI lux;

394 2800k) in comparison to darkness (28). In the present study, we used a polychromatic white,
395 blue-enriched light source of three different intensities (37, 92, 190 mel EDI; 6500k), i.e. the
396 lowest light level we used has similar mel EDI lux to the resting state study. It may be that
397 the amygdala sees its activity increase or decrease in response to light depending on
398 illuminance and spectrum, depending potentially on the type of retinal photoreceptor
399 recruited.

400 In terms of photoreceptors, we cannot conclusively say that the ipRGCs are underlying the
401 decrease in activity in the subparts we see at higher light levels. Given the projection of
402 ipRGCs to the medial amygdala reported in rodent and the light level we used, their
403 implication is very likely. Rods and cones may however also be contributing, and there may
404 be differential recruitment of photoreceptors at different illuminance levels (48). Future
405 studies in humans could determine the photoreceptor underlying the impact of light on
406 emotion processing and affective state this by using, for instance, silent substitutions and
407 metameric light exposures to selectively affect one photoreceptor type (49).

408 Emotional regulation is vital and evolutionary critical. The amygdala fulfils part of this
409 regulation to allow adaption to the changing environment. We find that several subregions
410 of the amygdala, including the medial nucleus that receive direct projection from ipRGCs,
411 showed a reduction of activity with increasing illuminance when processing emotionally
412 charged stimuli. We speculate that it is through the medial nucleus that light affect emotion
413 emotional state in healthy individuals as well as in patients in which different amygdale
414 nuclei may contribute to disorders (25,50–55).

Tables

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

Main GLMM			
Effect	**F Value**	**P value***	**Partial R^2**
Amygdala subpart	4.79	**<.0001**	**0.07**
Task	27.93	**<.0001**	**0.05**
Amygdala subparts x stimulus type	0.97	0.4	-
Age	1.18	0.28	-
Sex	1.01	0.32	-
BMI	0.17	0.68	-
Significant Pairwise comparisons			
Contrast#	**t-value**	**$P_{uncorrected}$**	**$P_{corrected}$**
1 vs. 3	2.2	**0.02**	0.45
1 vs 5	2.54	**0.01**	0.24
2 vs 3	2.09	**0.03**	0.53
2 vs 5	2.44	**0.01**	0.3
3 vs 4	-2.89	**0.004**	0.10
3 vs 6	-2.88	**0.004**	0.11
3 vs 8	-3.89	**0.0001**	**0.004**
3 vs 10	-3.45	**0.0006**	**0.02**
4 vs 5	3.24	**0.001**	**0.04**
4 vs 7	2.46	**0.01**	0.29
4 vs 9	2.57	**0.01**	0.23
5 vs 6	-3.22	**0.001**	**0.04**
5 vs 8	-4.23	**<.0001**	**0.001**
5 vs 10	-3.79	**0.0002**	**0.006**
6 vs 7	2.44	**0.01**	0.30
7 vs 8	-3.45	**0.0006**	**0.02**
7 vs 10	-3.01	**0.002**	0.08
8 vs 9	3.55	**0.0004**	**0.01**
9 vs 10	-3.11	**0.001**	0.06

For the full post hoc table, refer to Suppl. Table S3

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

Main GLMM			
Effect	**F Value**	**P value***	**Partial R^2**
Task stimuli	17.68	**<.0001**	**0.03**
Illuminance	11	**<.0001**	**0.02**
Amygdala subpart	1.63	0.10	-
Illuminance x Task stimuli	4.66	**0.001**	**0.008**
Task stimuli x Amygdala subpart	0.71	0.70	-
Illuminance x Amygdala subpart	1.42	**0.04**	**0.02**
Illuminance x Amygdala subpart X Task stimuli	0.51	0.99	-
Age	0.72	0.40	-
Sex	0.2	0.65	-
BMI	1.77	0.19	-
Significant pairwise comparisons			
Amygdala subpart	**Contrast#**	**t-value**	**P_{-value}**
3	0 vs 190	3.42	**0.005**
3	0.16 vs 190	4.15	**0.0003**
3	92 vs 190	3.51	**0.004**
5	0 vs 190	3.8	**0.001**
5	0.16 vs 190	3.89	**0.001**
5	37 vs 190	2.95	**0.02**
5	92 vs 190	3.3	**0.008**
7	0 vs 190	3.18	**0.01**
7	0.16 vs 190	2.79	**0.04**
9	0 vs 190	4.46	**<.0001**
9	0.16 vs 190	4.09	**0.0004**
9	37 vs 190	4.5	**<.0001**
9	92 vs 190	3.8	**0.001**

Illuminance is reported in mel EDI lux. For the full post hoc table, refer to Suppl. Table S4.

Data and code 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).

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