Luxotonic signals in human prefrontal cortex: A possible substrate for effects of light on mood and cognition

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Abstract

Light impacts mood and cognition of humans and other animals in ways we are only beginning to recognize. These effects are thought to depend upon a specialized retinal output signal arising from intrinsically photosensitive retinal ganglion cells (ipRGCs) that is being dedicated to a stable representation of the intensity of environmental light. Insights from animal studies now implicate a previously unknown pathway in the effects of environmental light on mood. A subset of ipRGCs transmits light-intensity information to the dorsothalamic perihabenular nucleus, which in turn, innervates the medial prefrontal cortex that plays a key role in mood regulation. While the prefrontal cortex has been implicated in depression and other mood disorders, its ability to encode the level of environmental light (luminance) has never been reported. Here, as a first step to probing for a similar retino-thalamo-frontocortical circuit in humans, we used functional magnetic resonance imaging (fMRI) to identify brain regions in which activity depended on luminance level where activity was modulated either transiently or persistently by light. Twelve brain regions altered their steady-state activity according to luminance level. Most were in the prefrontal cortex or in the classic thalamocortical visual pathway; others were found in the cerebellum, caudate, and pineal. Prefrontal cortex and pineal exhibited reduced BOLD signal in bright light, while the other centers exhibited increased BOLD signals. The light-evoked prefrontal response was affected by light history and closely resembled those of ipRGCs. Although we did not find clear correspondence between the luxotonic regions in humans and those in mice, the persistence and luxotonic nature of light-evoked responses in the human prefrontal cortex may suggest that it receives input from ipRGCs, just like in the mouse. We also found seventeen regions in which activity varied only transiently with luminance level. These regions, which are involved in visual processing, motor control, and cognition, were in the cerebral cortex, diverse subcortical structures, and cerebellum. Therefore, our results demonstrate the effects of light on diverse brain centers that contribute to motor control, cognition, emotion, and reward processing.

Introduction

Light impacts mood and cognition of humans and other animals in ways we are only beginning to recognize. Abnormal lighting regimes induce depression[1-4]. Bright light enhances antidepressant therapies, ameliorating both seasonal and non-seasonal depression[5-11]. Bright light affects decision-making and working memory, key functions of the prefrontal cortex[12-15]. These effects are thought to depend upon a specialized output channel of the retina dedicated to a stable representation of environmental illumination – a luminance signal[16-19]. This retinal output signal arises from intrinsically photosensitive retinal ganglion cells (ipRGCs), a rare class of output neuron that is autonomously sensitive to light by virtue of its expression of the photopigment melanopsin[20,21].

Light-intensity signals from ipRGCs are used by the brain to synchronize the circadian clock, constrict the pupil, and regulate neuroendocrine rhythms, learning[10,22,23], and mood[9]. Other RGCs ('*conventional RGCs'*) do not express melanopsin or encode ambient light intensity. Whereas ipRGCs have a maintained discharge that faithfully encodes irradiance, conventional RGCs respond to alterations in light intensity only briefly; their maintained firing rates are not correlated with photon flux[24-27]. In other words, conventional RGCs encode temporal and spatial contrast while ipRGCs encode integrated intensity. Conventional RGCs support the detection and recognition of objects, color, depth and motion[28-30] especially via their signals routed through the thalamus to the visual cortex.

New insights from animal studies now implicate a previously unknown pathway in the effects of environmental light on mood[31]. A subset of ipRGCs transmits light-intensity information to a newly identified region of the dorsal thalamus – the perihabenular nucleus (PHb). Neurons in this nucleus innervate the ventromedial prefrontal cortex (vmPFC) which plays a key role in mood regulation[32-34]. This circuit is necessary and sufficient for the induction of depression by abnormal lighting[31]. This retino-thalamo-frontocortical (RTFC) pathway is completely separate, much smaller, and radically different from the main retino-thalamo-visuocortical (RTVC) pathway that targets the visual cortex through the dorsal division of the lateral geniculate nucleus (dLGN) and superior colliculus (SC). Note that the PHb has been shown to also project to the nucleus accumbens that modulates hedonic behaviors [35].

These findings imply that a retinal signal of integrated light intensity from ipRGCs is routed to the prefrontal cortex through a remarkably direct pathway. Does a similar pathway exist in humans? Humans too have intensity-encoding ipRGCs with highly conserved functional roles[36-38]. And, like mice, human studies have revealed links among prefrontal cortex, mood[5,39-46], and light exposure[6,7]. While the PFC has been implicated in depression and other mood disorders [47-50], the ability of the prefrontal cortex to encode the level of environmental luminance has never been reported. Identifying such a pathway and understanding its function might directly promote development of approaches to treat depression, either by pharmacological manipulation of activity in selected nodes of the pathway, or environmental manipulation with targeted bright light therapy.

Here, as a first step to probing for a RTFC circuit in humans, we tested the simple hypothesis that the intensity of light reaching the eyes, stripped of color, form and movement information, would modulate activity in human prefrontal cortex. Our findings support the hypothesis. Ambient light intensity does indeed tonically modulates the prefrontal cortex in a dose-dependent manner. We used functional magnetic resonance imaging (fMRI) to identify brain regions in which activity depended on luminance level (hereafter 'luxotonic regions') where activity was modulated either transiently or persistently by light. Altogether, twelve brain regions altered their steady-state activity according to illuminance level. Most were in the prefrontal cortex or in the classic thalamocortical visual pathway; others were found in the cerebellum, caudate, and pineal. Prefrontal cortex and pineal exhibited reduced BOLD signal in bright light, while the other centers exhibited increased BOLD signals. The time course of the light-evoked responses in prefrontal cortex most closely resembled those of ipRGCs. The prefrontal response was also affected by light history. We also found seventeen regions in which activity varied only transiently with luminance

level. These regions, which are involved in visual processing, motor control, and cognition, were in the cerebral cortex, diverse subcortical structures, and cerebellum.

Results

To determine whether a luminance-dependent functional pathway affects human frontal cortex, we used BOLD fMRI (3T Siemens Prisma, 2 mm isotropic voxels) to explore whole-brain activation patterns in 20 healthy participants viewing full-field diffused light stimuli. Every 30 sec, the light was stepped to one four possible luminance levels. Overall, these spanned nearly four orders of magnitude (10.2, 12.1, 13.1, and 13.8 log photons cm^{-2} s^{-1}). Intensities were randomized except that a given intensity never appeared in consecutive epochs. Each intensity was presented 15 times (Supplementary Fig. 1A,B). Participants donned Teflon goggles that diffused the light and removed any spatial contrast. To monitor the level of alertness throughout the experiment, we required participants to discriminate between two tones by pressing one of two buttons (Supplementary Fig. 1A). We used a combination of criteria to reveal brain regions that exhibited activity that varied monotonically with luminance level and showed either a sustained or transient component (Supplementary Fig. 1C,D) (see *Methods* for details).

Diffuse luminance modulates steady-state activity of diverse cortical, subcortical, and cerebellar regions

Overall, 12 brain regions met the criteria for luminance-dependent monotonic activation with a significant sustained component (see methods for details on the regressor used for the analysis). Luminance-dependent activation level in all regions persisted throughout the 30-sec duration of the stimulus, and in several regions, also changed abruptly upon light onset. Steady-state BOLD signal either monotonically increased or decreased with luminance level in those regions (Fig. 1). Six of these were located in the prefrontal cortex, and included the anterior prefrontal, orbitofrontal, and anterior cingulate cortices (regions S1-S6). The BOLD response to diffuse light as well as the signal's dependence on luminance level was inverted in the primary visual system. Light strongly increased the BOLD signal in the occipital lobe, especially in the primary visual cortex. The zone of activation may have extended beyond V1 into a number of extrastriate regions too, but many extrastriate regions lacked detectable modulation. The LGN, the thalamic relay nucleus of the primary visual pathway, is almost certainly the source of this luxotonic signal in V1. It too, exhibited bilateral, strong BOLD activation responses to bright diffuse light, responses that monotonically increased with luminance level. The only brain region outside the primary visual pathway to share the visual system's BOLD activation by light was a small region in the uvula at the inferior vermis of the cerebellum. Two additional small regions exhibited suppressive BOLD responses that monotonically decreased with luminance, like those in the prefrontal cortex. These were the right caudate nucleus and the pineal, which is known to be negatively regulated by light through the influence of ipRGCs[51].

Functional connectivity between luxotonic sustained regions

We next assessed whether the activated regions formed independent or dependent networks by assessing functional connectivity (Pearson correlation) between each of the 12 regions that exhibited sustained luminance-dependent activity (Fig. 2A). BOLD time-series in luxotonic regions at the frontal cortex generally exhibited significant correlations with one another (Fig. 2A, hot colors), with the exception of the left middle frontal gyrus that was located posteriorly to all other analyzed prefrontal regions. Similarly, we found positive correlations in the BOLD time-series among the regions in the RTVC: V1 (with extra striate areas) and LGN as well as a region in the vermis of the cerebellum. These BOLD time-series were not correlated with prefrontal cortical regions (Fig. 2A, cold colors). Thus, it seems that sustained luminance-related responses engaged two separate functional networks, one encompassing RTVC-related regions and another including a set of prefrontal cortical regions previously implicated in high-level cognition and value-related judgments. This is the first demonstration that a cortical area other than the visual cortex modulates its activity in proportion to luminance level. To start studying the temporal profile of light-

evoked BOLD responses, we normalized all the BOLD time courses to range between 0 and 1 (or -1) (Fig. 2B). Luxotonic regions in which light enhanced the BOLD signal showed a relatively fast (latency 10 sec) increase in BOLD responses with a transient peak, which then gradually declined in magnitude ('transient group', n = 4). This group comprised luxotonic regions in the visual cortex, LGN, and cerebellum. In contrast, luxotonic regions in which light suppressed the BOLD signal exhibited a slowly and gradually developing negative response that reached its minimum toward the end of the 30-sec stimulus presentation ('persistent group', n = 8). This persistent group included all the prefrontal luxotonic regions as well as those in the caudate nucleus and pineal. This dichotomy in the temporal profile and polarity of the responses is also evident when plotting the time to peak/trough as a function of the slope before peak/trough (Fig. 2C).

Light suppresses steady-state prefrontal cortex activity

Next, we aimed at exploring the ability of the prefrontal cortex to encode luminance. To avoid any effect of prior light exposure on BOLD activity, we focused on the three transitions in which luminance level (L) was stepped up from the lowest intensity, that is, L1 → L2, L1 → L3, and L1 → L4. This revealed that prefrontal activity in response to all luminance levels developed slowly throughout the 30-sec duration of the stimulus and decreased monotonically with increasing luminance (Fig. 3, left panels). Steady-state prefrontal activity, measured as the average response over the last 10 sec of the 30-sec stimulus, monotonically decreased with increasing luminance level in all six identified prefrontal luxotonic regions (Fig. 3, panels on second column from the left). These included the left and right superior frontal gyri (S1,S2), right orbital gyrus (S1), left and right middle frontal gyri (S3,S4), right anterior cingulate cortex (S5), and subgenual anterior cingulate cortex (S6). Therefore, the 6 identified prefrontal regions encode steady-state luminance level, just as ipRGCs do. Activity in two additional luxotonic regions, in the epithalamic pineal (S11) and right striatal caudate (S10), also monotonically decreased with increasing luminance (Supplementary Fig. 2A,B).

Light enhances steady-state activity along the thalamo-visuocortical pathway

Fig. 4A shows the effect of light exposure on activity along the thalamo-visuocortical pathway. In the visual cortex (S7), activity increased sharply several seconds after the light onset, and then gradually rolled off but never returned to baseline during the 30-sec light stimulus (Fig. 4A, left column). Similar trends were observed also in the left (S8) and right (S9) LGN (Fig. 4B,C, left column). The magnitude of responses in the visual cortex was twice as large as in the LGN. Steady-state activity in the three identified regions along the thalamo-visuocortical pathway increased with luminance (Fig. 4A-C, second column from left). Activity in another luxotonic region, in the cerebellar vermis (S12), also appeared to slightly increase with increasing luminance (Supplementary Fig. 2C).

Light-evoked activity in the prefrontal cortex is more persistent than along the thalamo-visuocortical pathway

To study the persistence of light-evoked responses, we calculated a persistence index (ratio between the response over the last and first 10 sec of the stimulus, for all step-up transitions). Persistence in the prefrontal cortex was significantly higher than along the thalamo-visuocortical pathway (permutation t-test, $p = 0.02$) with mean±s.d. persistence index across the 6 prefrontal regions being 0.62±0.08 compared to 0.44±0.06 along the thalamo-visuocortical pathway (Fig. 5A). Furthermore, sensitivity, calculated as the difference in steady-state response between the lowest and highest stimulus luminance divided by the change in luminance, was largest in the right superior frontal gyrus, subgenual anterior cingulate, and visual cortex (Fig. 5B).

Effect of light history on prefrontal activity

To test the effect of prior light exposure on BOLD activity, we plotted the three transitions in which luminance level was stepped down from the highest luminance level, that is, L4 → L1, L3 → L1, and L2 → L1 (Fig. 3, third column from left). Then, we fit a straight line to the activity around a given transition

and repeated this for the three step-up transitions (Fig. 3, left panels) and the three step-down (Fig. 3, third column from left). This yielded three slope values for step-up transitions and three slope values for step-down transitions (Fig. 3 right). If brain activity is not affected by prior light exposure, the trend observed when moving across slope values should be opposite for the step-up and step-down transitions. Deviation from this expectation serves as a proxy for the strength of the effect of prior light exposure. While activity in all 12 identified luxotonic regions was affected by prior light exposure, the effect was largest in the right and left superior frontal gyri and subgenual anterior cingulate gyrus (Fig. 5; Fig. 3, right; Fig. 4, right; Supplementary Fig. 2, right). These results demonstrate a strong effect of light history on prefrontal activity. ipRGCs, more than any conventional ganglion cell, are known to be capable of continually responding following the light offset[52]. Therefore, this analysis also suggests that ipRGCs contribute to light-evoked prefrontal activity, at least in the right and left superior frontal gyri and subgenual anterior cingulate gyrus.

Luminance modulates transient activity in the cortex, subcortex, and cerebellum

In addition to the 12 luxotonic regions with a significant sustained component that we identified above, we also identified 17 regions which exhibited luminance-dependent monotonic activation with a significant transient component (see methods for details on the regressors used for the analysis). Activation either monotonically increased (orange) or decreased (blue) with luminance (Fig. 6). Luminance-dependent activation was detected bilaterally in the superior medial frontal gyri (T1, T2), precentral gyri (T6, T7), visual cortex T13), and paracentral lobule (T11). Luminance-dependent activation was restricted to the right hemisphere in the supplementary motor area (T5), frontal operculum (T8, T9), parietal operculum (T10), and insula (T12). In contrast, left-hemisphere-only activation was detected in the middle frontal (T3), anterior cingulate (T4), middle occipital (T14), and inferior occipital (T15) gyri, and cerebellum (T16, T17).

Functional connectivity between transient luxotonic regions

We next assessed whether the 17 transiently activated luxotonic regions formed independent or dependent networks by assessing their functional connectivity (Fig. 7). BOLD time-series in the frontal cortex showed two distinct activity groups, one in the prefrontal cortex (group a) and another in more posterior regions including motor areas (group b). Time-series in the latter group correlated with those in the parietal operculum. Time-series in the paracentral lobule (groups c) positively correlated with those in the prefrontal clusters but negatively correlated with all other regions. Time-series in the left inferior occipital gyrus did not correlate with any of the other regions (group d). Time series in the visual cortex and left Middle occipital gyrus correlated with one another.

Light transiently modulates cortical and cerebellar activity

Next, just as we did for luxotonic regions in which activity exhibited a sustained component (Figs. 3 and 4, Supplementary Fig. 2), we studied the luminance encoding capability of the 17 identified luxotonic regions that exhibited a significant transient component. To this end, we examined the three transitions in which luminance level was stepped up from the lowest intensity (Supplementary Fig. 3). Luminance-dependent activation level in all regions changed abruptly upon light onset, and in several regions, persisted throughout the 30-sec duration of the stimulus. Activity in the superior medial and middle frontal gyri as well as in the anterior cingulate cortex (regions T1-T4) decreased sharply upon light onset, stayed relatively stable throughout the 30-sec duration of the stimulus, and typically decreased monotonically with increasing luminance. Activity in the 13 remaining identified regions increased upon light onset and then gradually rolled off. In some regions (e.g., visual cortex, T13) activity did not return to baseline during the 30-sec light stimulus.

Luxotonic regions that show both sustained and transient activation components were restricted to a well-defined streak in the occipital lobe

Finally, we examined the overlap between luxotonic regions in which activity showed significant sustained and transient components. Sustained activation comprised 4,766 voxels and transient activation comprises 3,403 voxels. The combined activation was 7,484 voxels. Overlap between luxotonic regions that showed

transient and sustained activation was 685 voxels, corresponding to ~9% of the area of combined activation. Interestingly, sustained and transient response regions were almost completely segregated, except for one nearly contiguous strip running along the parieto-occipital sulcus and the dorsal cuneus (Fig. 8), This region might be in a position to modify information transferred from the primary visual cortex to extrastriate cortices[53].

Discussion

This study mapped for the first time where in the human brain integrated activity is related to luminance. We identified 29 brain regions in which activity varied monotonically with luminance. Activity in 12 regions exhibited a significant sustained component and activity in 17 regions exhibited a significant transient component. Considering the conservative criteria used in identifying luxotonic regions, the large number and diversity of identified brain regions in which activity monotonically depended on luminance level is truly remarkable. While luxotonic responses in the LGN[54-57] and visual cortex[58-62] along the thalamo-visuocortical pathway have been previously documented, to the best of our knowledge, this is the first report of luxotonic activity in the prefrontal cortex, precentral gyri, paracentral lobule, frontal and parietal operculum, insula, supplementary motor area, caudate nucleus, pineal, and cerebellum. Therefore, our results demonstrate the effects of light on diverse brain centers that contribute to motor control, cognition, emotion, and reward processing.

Acute effect of light on steady-state prefrontal cortex activity

Past research has suggested the light-evoked modulation of several prefrontal regions. For example, blue (as opposed to green or orange) light exposure concurrent with an auditory working memory task has been shown to increase activity in the left middle frontal gyrus[12,13] and decrease ACC activity[13]. Furthermore, blue (as opposed to amber) light has been reported to decrease ACC activation following an emotional anticipation task[63]. However, this study is the first to demonstrate wide-ranging effect of light in the prefrontal cortex, an effect that monotonically varied with luminance level. We identified six luxotonic regions with a sustained-activity component in the prefrontal cortex: right and left superior frontal gyri, right and left middle frontal gyri, right anterior cingulate cortex, and subgenual anterior cingulate cortex. These brain regions are involved in a large number of cognitive and emotional processes. For example. the left superior frontal gyrus is involved in self-awareness[64], laughter[65], and spatial working memory[66,67]. In the right hemisphere, this region contributes to the control of impulsive response or the inhibition of action[68]. The middle frontal gyrus is thought to be involved in the regulation of working memory[69] and reorienting attention[70], and to be part of the Ventral Attention Network[71] – a bottom-up system that responds to unexpected stimuli in an involuntary manner[72]. Moreover, the left middle frontal gyrus contributes to literacy while its right counterpart is strongly associated with numeracy[73]. The anterior cingulate cortex (ACC) contributes to social cognition, attention allocation, motivation, decision making, learning, cost-benefit calculation, ethics and morality, impulse control, and emotion (reviewed in [74-77]). And, finally, the subgenual ACC has been associated with the regulation of emotions and the mechanism of action of antidepressant medication (reviewed in[78]). Our results demonstrate that activity in all six identified prefrontal luxotonic regions decreased with luminance, indicating the potential role of light exposure in modulating a myriad of cognitive and affective processes.

Effects of prior light exposure on prefrontal activity

In addition to the acute and almost instantaneous effect of light on concurrent neural activity (discussed above), light exposure can also affect subsequent neural activity. For example, a single, 30-min exposure to blue light has been shown to improve working memory task performance and increase neural activation in the dorsolateral (dlPFC) and ventrolateral (vlPFC) prefrontal cortex over the subsequent 40-min period[79]. Another study, used a shorter light exposure (21 min) and reported increased activation over the subsequent 8-min period in the right insula, right posterior cingulate, right superior parietal lobe, right dlPFC (likely

middle frontal gyrus), and right fusiform gyrus[80]. Additionally, light exposure before but not after learning has been demonstrated to improve memory consolidation at night[81]. Our results indicate a pronounced effect of light exposure on subsequent activity in the right and left superior frontal gyri and the right orbital gyrus. We show that activity in those regions, which comprise a portion of the ventromedial prefrontal cortex (vmPFC), is suppressed during light exposure as well as following it. Therefore, light exposure may modulate activity in the vmPFC that plays a key role in the regulation of decision making, social behavior, working memory, and mood[49].

Origin of prefrontal luxotonic responses

The persistent responses we observed in the prefrontal cortex are reminiscent of the responses of intrinsically photosensitive retinal ganglion cells (ipRGCs) – they persist throughout the duration of the stimulus and even following light offset, with the duration of these post-stimulus persistent responses increasing with luminance[52]. This suggests a substantial contribution of ipRGCs' light responses to prefrontal activity. Previous reports that examined the effect of blue light on functions that are mediated by the prefrontal cortex support this claim. For instance, evening blue-enriched white light (as opposed to white light), either in the environment or emitted by a computer screen, improves cognitive performance[82,83], alertness[82,83], and concentration[82]; it also alters sleep structure[84] and reduces evening sleepiness[82,83] and EEG low-frequency activity (1–7 Hz) in frontal brain regions[83,84]; improvement in cognitive performance under blue-enriched lighting has been reported also during the day[85]. Together, these reports suggest that alteration in cognition and frontal brain activity involves the pathways that are driven by the blue-light-sensitive ipRGCs. Lastly, in visually blind individuals who lack rod/cone photoreceptors but retain ipRGCs, blue light exposure during an auditory task has been shown to stimulate activity in the medial prefrontal cortex and ventrolateral PFC, supporting the contribution of ipRGCs to the light-evoked modulation we observed in the prefrontal cortex[86].

On the other hand, the transient responses we and others observed in the visual cortex[87] and LGN[88] are reminiscent of the responses of conventional RGCs – they gradually role off and terminate at light offset. Interestingly, responses in the visual cortex and LGN did not return to baseline by the termination of stimulus, suggesting a modest contribution of ipRGCs. Indeed, while the majority of input to dLGN, which routes information to visual cortex, arrives from conventional RGC, at least some ipRGC types do project to dLGN[89]. Moreover, melanopsin, the blue-sensitive pigment of ipRGCs, has been shown to contribute to light-evoked response in the visual cortex[60]. Therefore, the light-evoked activity we observed in the visual cortex and LGN likely represent the integration of signals from both ipRGCs and conventional RGCs.

Our results suggest no clear correspondence between the luxotonic regions in humans and those in mice. In the mouse, the thalamic PHb has been shown anatomically to project to the infralimbic and prelimbic cortices[31], raising the possibility that luxotonic neural input is transmitted from the PHb to those limbic cortices. However, in the current study, no luxotonic activity was detected in the human infralimbic and prelimbic cortices. Indeed, our conservative criterion for minimum cluster size (27 voxels) and the relatively limited size of the human infralimbic and prelimbic cortices might have precluded the identification of luxotonic regions in these cortical areas. Thus, it is currently unknown whether the human prefrontal cortex is part of a pathway homolog to the RTFC pathway discovered in mice. Nevertheless, the persistence and luxotonic nature of light-evoked responses in the human prefrontal cortex strongly suggest that it receives input from ipRGCs, just like the RTFC pathway in the mouse[31]. Moreover, mouse PHb neurons that receive input from ipRGCs have been shown to be mainly GABAergic[35]. This suggest that the mouse PHb transmits inhibitory drive to the prefrontal cortex, and might explain our observation that light exposure suppresses prefrontal activity.

Prefrontal cortex and mood regulation

The prefrontal cortex (PFC) is commonly divided, based on connectivity and functional specialization, into the dorsolateral (dlPFC) and ventromedial (vmPFC)[90,91] and reviewed in Koenigs and Grafman[49]. Resting state brain activity[39-41] and glucose metabolic rates[41,42] in the vmPFC, including the subgenual ACC and

orbitofrontal gyrus, of depressed subjects have been shown to be higher than those of healthy subjects. In contrast, metabolic rates in the dlPFC of depressed (as opposed to healthy) subjects have been reported to be lower[41,43]. Recovery from depression and antidepressants affect the PFC in an opposite manner. That is, antidepressants and the accompanying recovery from depression have been associated with decreased activity in vmPFC but increased activity in dlPFC[44-46]. In the current study, we detected light-evoked suppression of prefrontal activity, including that in the subgenual ACC and orbitofrontal gyrus, as a function of luminance level. Therefore, just like antidepressants, light appears to act to reduce activity in the subgenual ACC and orbitofrontal gyrus, suggesting an antidepressive role for light in these regions.

Effect of light on the pineal, cerebellum, and caudate nucleus

We identified luxotonic regions in the pineal, cerebellum, and caudate nucleus. We found that light suppressed the activity in the caudate nucleus, and that the extent of suppression depended on luminance. The functional role of luminance-dependent modulation of the caudate nucleus is unknown. However, the luxotonic nature of the caudate raises the possibility light might affect the reward system, motor control, procedural and associative learning, and inhibitory control of action [92]. Indeed, long-term blue light exposure has been shown to enhance risk-related activity in the ventral striatum and head of caudate nucleus[93].

We identified a luxotonic region in the uvula that constitutes a large portion of the inferior vermis of the cerebellum. Activity in this region was enhanced with light exposure. The uvula has been shown to be activated during optokinetic eye movements, and this activity depended on the speed and direction of eye movements[94]. Interestingly, oculomotor performance has been shown to depend on the environmental luminance, resulting in eye movements of greater accuracy in the light[95]. Together, these findings suggest a possible functional role for the luminance-dependent activity of the uvula in oculomotor response.

The melatonin-producing pineal gland modulates sleep and circadian and seasonal rhythms (reviewed in [96]). The pineal receives indirect photic input from ipRGCs (via the paraventricular hypothalamic nucleus, intermediolateral nucleus of the spinal cord, and superior cervical ganglion) (reviewed in[97]). Light is known to reduce melatonin production[98], consistent with our observation that light exposure suppresses BOLD activity in the pineal in a luminance-dependent manner. Melatonin suppression by light is a common assay for the integrity of the non-image-forming visual system, and the spectral tuning of the effect of light on melatonin level is strikingly similar to that of melanopsin, rather than to rods or cones[99,100]. The suppression of melatonin by light is retained following severe degeneration of rods/cones, in both humans[101] and mice[102]. The similar form of the pineal and prefrontal light-evoked responses, and its contrast with light responses in the visual cortex and LGN, is yet another indicator for ipRGCs contribution to the observed suppression of prefrontal activity by light.

Transient effect of light on brain activity

While the focus of this report is the effect of light exposure on steady-state brain activity, our analysis identified 17 brain regions in which activity monotonically varied with luminance level and exhibited a significant transient component. The precentral gyrus (Fig. 7, T6, T7), the site of the primary motor cortex, together with the supplementary motor area (T5)[103], paracentral lobule (T11)[104] and other structures are involved in the planning, regulation, and execution of voluntary movements. The paracentral lobule is also involved in somatosensory processing[104]. The frontal operculum (T8, T9) is a critical node in a network controlling activity in other brain areas to perform the wide array of cognitive tasks[105,106]. The frontal operculum is frequently coactivated with other frontal regions, and its activity can predict how well a subject will perform selected subsequent cognitive tasks[107]. The inferior occipital gyrus (T15) has been shown to contribute to the processing of facial features[108,109]. The middle occipital gyrus (T14) is involved in the processing of visual spatial information[110]. The parietal operculum (T11) is the site of the secondary somatosensory cortex (SII), being involved in the perception of vibration, light touch, pain and visceral sensations (reviewed in [111]). The insular cortex plays a central role in the regulation of the body homeostasis. It is the site of the primary gustatory cortex, it is involved in the perception of visceral sensation, and it

receives auditory, olfactory, vestibular, and somatosensory input from diverse association areas. The insular cortex (T14) is being innervated by prefrontal centers such as the anterior orbitofrontal cortex and the prefrontal cortex, and limbic structures, including the cingulate gyrus and amygdala (reviewed in [112]). As such, the insular cortex is heavily involved in cognitive and emotional processes. Our identification of luxonic regions in the above-mentioned cortical and subcortical brain areas suggests that light might affect at least some of these brain centers, and possibly modulate a remarkable array of sensory, motor, emotional, cognitive, and homeostatic functions.

Other sources of time-locked increases in brain activity

Eye movements or blinking, possibly coinciding with the onset of the light stimulus, might have induced the observed time-locked activation increase is several brain regions. The cortical areas involved in eye movements control have been reported to include the frontal eye field, supplementary eye field, posterior parietal lobe, dorsolateral prefrontal cortex which lies in the middle frontal gyrus, and the anterior and posterior cingulate cortex[113]. Consequently, one of the luxotonic transiently-modulated regions, the middle frontal gyrus, might be associated with eye movements (Fig. 7, T3). Eye blinking might potentially represent another confounding factor. However, eye blinks have been shown to be associated with activity increases in the anterior cingulate gyrus, right inferior frontal gyrus, right superior temporal gyrus, left superior temporal gyrus, and cuneus[114], but not with activity modulation in any of the 17 luxotonic regions identified in the current study as exhibiting a significant transient component (Fig. 7). Taken together, aside from the transient luxotonic regions identified in the middle frontal gyrus, all other regions identified in the current study most likely represent a true luxotonic behavior. In summary, the current study demonstrates the time-locked, luminance-dependent effect of light exposure on the activity of brain centers that mediate a large number and diverse functional roles. In several regions, activity is enhanced with increasing luminance level, while in others, activity is suppressed. In some regions, the effect of light is brief, while in others, the effect of light persists for the entire duration of the stimulus and even longer. We are hopeful that this study will light up the way toward better appreciation of the diverse effects of ambient lighting on the physiology and behavior of animals and humans, and ultimately promote the development of therapies and guidelines to enhance health and wellness.

Methods

Functional magnetic resonance imaging (fMRI)

We used BOLD functional MRI [3T Siemens Prisma, 2 mm isotropic voxels, repetition time (TR) 2 sec] to explore whole-brain activation patterns of 20 healthy participants (age 20-40 years old) in response to full-field diffused light stimuli. Participants underwent five runs each, with each run consisting of three groups of blocks, where each group contained all four luminance levels in pseudorandom order (10.2, 12.1, 13.1, and 13.8 log photons cm^{-2} s^{-1}; 30 sec epochs). Visual stimulus was presented using a digital light processing (DLP) projector (Optoma EP719) coupled with a plano-convex lens that focused the light onto the mirror of the headcoil. Participants were wearing Teflon goggles to diffuse the light and remove any patterns from the stimulus. To monitor the level of alertness, subjects were asked to perform an auditory discrimination task; they needed to discriminate between two tones by pressing on one of two buttons. Luminance level was measured at the plane of the subjects' eyes using a fiber-coupled (core diameter 1000µm, 0.5 NA; Ocean Optics) absolute-irradiance-calibrated spectrometer (USB4000-UV-VIS-ES, Ocean Optics).

We did not pharmacologically control pupil size. Thus, the participants' pupils likely constricted or dilated dependent on stimulus luminance. Increased luminance leads to pupil constriction and restricts the amount of light reaching the retina. But this happens within the first 1-2 first seconds upon light onset, dependent on luminance level[115]. This should theoretically diminish the light-evoked activity in the LGN and visual cortex. Instead, in our setup, increased luminance led to greater activation in the LGN and visual cortex.

Therefore, if anything, not controlling for pupil size might have led to an underestimation of the true activity modulation in response to light.

Spatiotemporal processing of fMRI data

Non-linear warping was used for anatomical alignment. The surviving anatomical detail, including for subcortical regions indicates a robust alignment. Individual data were slice-time and motion corrected, spatially smoothed (4 mm kernel), and normalized to Montreal Neurological Institute (MNI) space.

Identification of luxotonic brain regions

We used a combination of criteria to reveal brain regions whose activity varied monotonically with luminance level and exhibited either a significant transient component or a significant sustained component. Each 30 sec stimulus block was modeled with a pair of regressors, one transient and one sustained [87], using a Generalized Least Squares approach with restricted maximum likelihood estimation of the temporal auto-correlation structure. The transient regressor convolved the hemodynamic response function (HRF) with a 1 sec stimulus event occurring at the transition time from one stimulus intensity to the next, allowing us to capture transient onset and offset responses, which are known to occur for luminance level increments. Transient responses may be produced by both luminance onsets and luminance offsets. Because the initial response at each luminance transition includes both the onset response for the current luminance level and an "offset" response for the previous level, an additional parametric regressor was used for the transients. The parametric regressor varied linearly in amplitude according to the absolute value of each luminance increment or decrement; that is, luminance increments and decrements were both assumed to produce a transient effect of similar magnitude and polarity that varied according to the size of the step. The sustained regressor convolved the HRF with the entire 30 sec stimulus period and allowed us to estimate sustained light-evoked responses independently of any transient onset or offset responses. Modeling our data using these transient and sustained regressors yielded more stable results compared to modeling with TENT functions at each (repetition time) TR because it involves the fitting of only one parameter (beta coefficient) for each block function, as opposed to fitting separate parameters for each of the 15 individual TENT functions. Finally, data were modeled using a third regressor, corresponding to the presentation of the auditory stimuli. We did not analyze the response to auditory stimuli separately but instead treated it as nuisance effect. Moreover, a linear contrast was used to identify voxels having monotonically increasing or monotonically decreasing responses according to luminance levels. Group level ANOVA was run with effects calculated based on the coefficients from the single subject contrasts, and clusters were identified using a voxel wise significance of $p<0.001$ and a family wise error (FWE) of 0.05 (minimum cluster size = 27 voxels). A small volume correction was performed to find the same FWE only for thalamic regions (minimum cluster size = 9 voxels), which did not otherwise survive the full brain false discovery rate (FDR) correction.

Luminance-Response (LR) curves were calculated using the early phase of response (R_0) for brain regions that exhibited a significant transient component, and using the late, steady-state, phase of response (R_s) for brain regions that exhibited a significant sustained component. These early and late response phases were taken as the mean BOLD activity over the first and last 10 sec of the 30 sec visual stimuli, respectively. To quantify how persistent the response is in relative terms, we calculated a persistence index: R_s/R_0 in response to the highest luminance stimulus (L4). A persistence index of 0 indicates that brain activity returned the baseline by the termination of the stimulus (a perfectly transient response). Whereas, a persistence index of 1 indicates that brain activity remained constant throughout the stimulus duration (a perfectly sustained response). The sensitivity of a brain region to light was calculated as the difference in steady-state response (R_s) between the second lowest (L2) and highest (L4) stimulus luminance divided by the change in luminance (1.7 log photons cm^{-2} s^{-1}). All data were analyzed using custom Matlab scripts.

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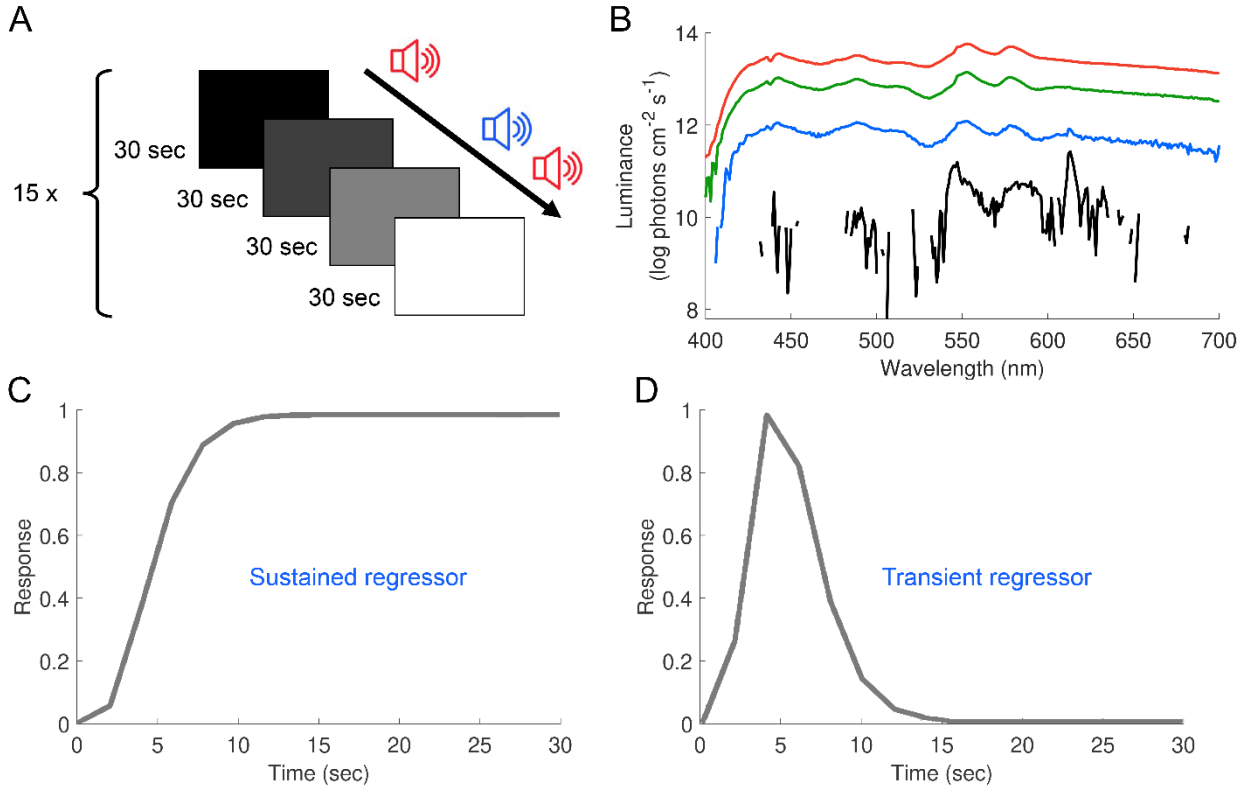
Figures and Legends



Supplementary Figure 1.

(A) Experimental protocol. Each participant underwent five runs, with each run consisting of three groups of blocks, where each group consisted of 30-sec full-field diffused light stimuli at four luminance level levels presented in pseudorandom order. Throughout the protocol participants were asked to perform an auditory discrimination task – to discriminate between two tones, presented in pseudorandom order, by pressing on one of two buttons. This allowed to monitor the participants' level of alertness. (B) Spectra of the four visual stimuli. Missing data in the spectra of the lowest luminance level (black) represent spectral ranges in which luminance was too low to be detected by the spectrophotometer. (C,D) Each 30 sec stimulus block was modeled with a pair of regressors: (1) a sustained regressor with a 30 sec stimulus event, covering the entire 30 sec stimulus period, and (2) a transient regressor with a 1 sec stimulus event occurring at the transition time from one stimulus luminance to the next.

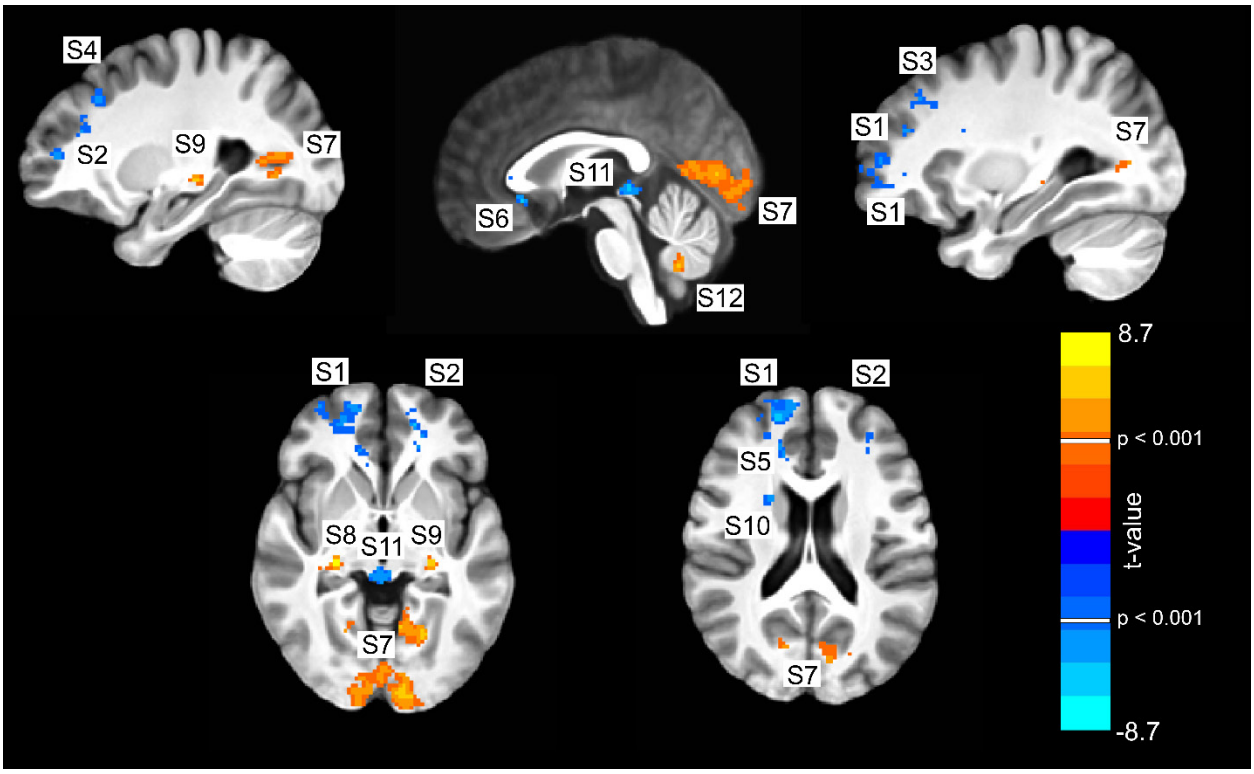


Figure 1. Cortical, subcortical, and cerebellar luxotonic regions that show a significant sustained component

The 12 identified luxotonic regions color-coded based on the contrast for monotonic increases or decreases as a function of luminance level. Color scale corresponds to *t*-value: warm colors (positive t-values) – light-evoked responses increases with luminance level; cool colors (negative t-values) – light-evoked responses decreases with luminance level. Color bar, *t*-values ranges ±8.7, and images are thresholded at $p < 0.001$, t(two-tailed) = 3.621 (white horizontal lines). Anatomical underlay represents the mean of all 20 subjects following spatial alignment.

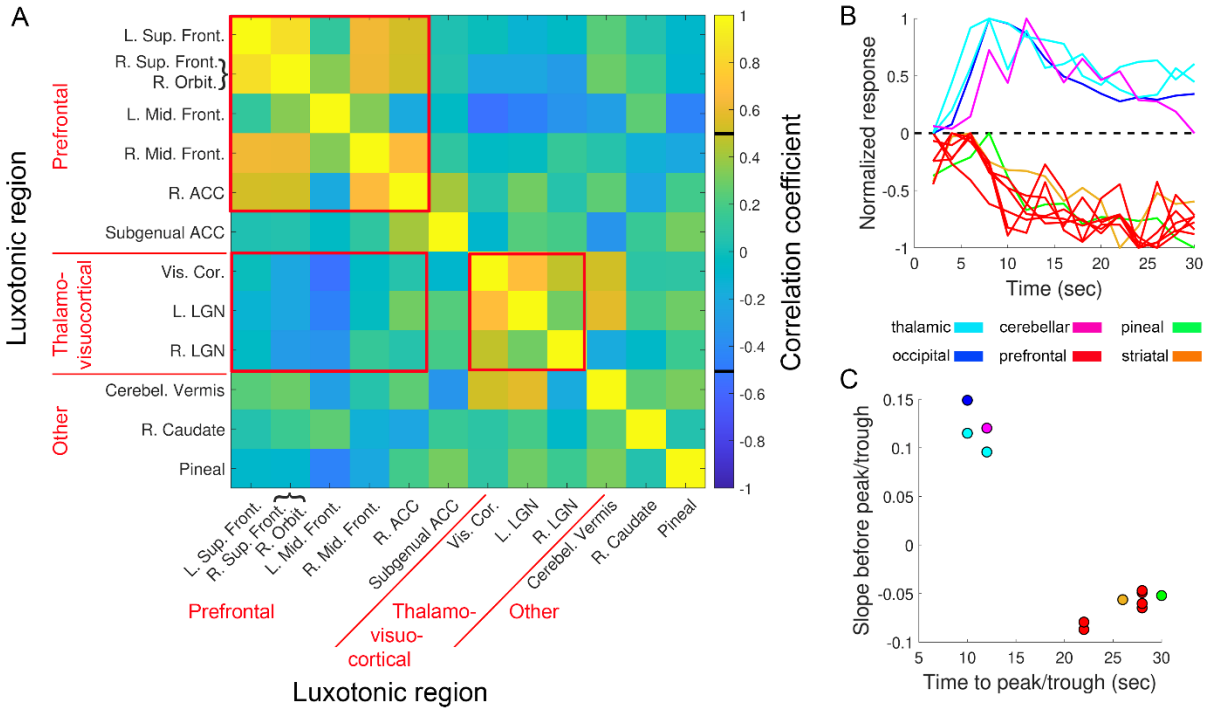


Figure 2. Light-evoked responses with a significant sustained component are either transient and increasing with luminance or persistent and deceasing with luminance

A. Pair-wise Pearson correlation between the 12 identified luxotonic regions. Regions are grouped as 'Prefrontal', 'Thalamo-visuo-cortical', and 'Other'. Correlation coefficient of ±0.51 corresponds to a significance level of 0.05 (indicated on the color scale bar). **B.** Normalized light-evoked responses to the highest-luminance level in all 12 identified luxotonic regions, averaged across 20 participants, fell into two functional groups: transient and persistent. Responses are color-coded based on the general brain region, as depicted in the legend at the bottom. **C.** Distribution of the 12 identified luxotonic regions as a function of the slope before peak/trough and the time to peak/trough. Responses are color-coded based on the general brain region.

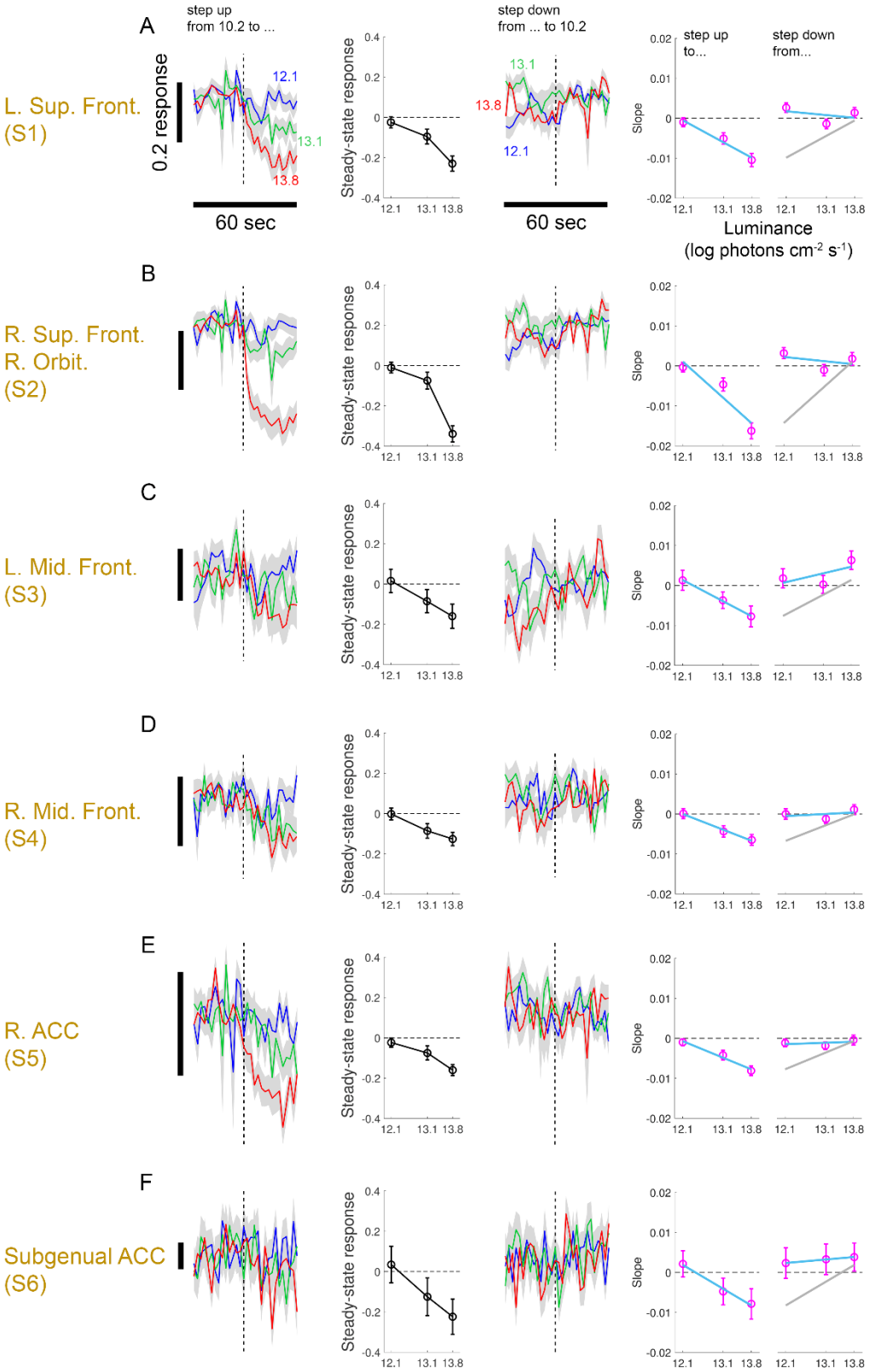

A
step up
from 10.2 to ...
step down
from ... to 10.2
step up
to...
step down
from...
L. Sup. Front.
(S1)
0.2 response
12.1
13.1
13.8
60 sec
60 sec
Steady-state response
Slope
Luminance
(log photons cm-2 s-1)
B
R. Sup. Front.
R. Orbit.
(S2)
C
L. Mid. Front.
(S3)
D
R. Mid. Front.
(S4)
E
R. ACC
(S5)
F
Subgenual ACC
(S6)

Figure 3. Light suppresses steady-state prefrontal activity

(A-F, left). BOLD Light-evoked responses to step up transitions – transitions in which luminance was stepped up from the same, lowest, luminance level. Responses around individual transitions are depicted in different colors. Shaded gray areas represent the standard error from the mean. Dashed vertical line marks the transition time. For example, the red curve in panel A represents stepping up luminance from the lowest level (L1, 10.2 log photons cm^{-2} s^{-1}) to the highest level (L4, 13.8 log photons cm^{-2} s^{-1}). (A-F, second column from left). Steady-state prefrontal activity monotonically decreased with increasing luminance level in all six identified prefrontal luxotonic regions. These are the left and right superior frontal gyri and right orbital gyrus (A,B), left and right middle frontal gyri (C,D), right anterior cingulate cortex (E), and subgenual anterior cingulate cortex (F). Vertical bar representing 0.2 BOLD response in (A) applies for the amplitude of responses in (A)-(F). (A-F, third column from left) BOLD Light-evoked responses to step down transitions – transitions in which luminance was stepped down from the same, highest, luminance level. (A-F, right) Slopes of lines fitted to the three step-up and three step-down transitions. In the prefrontal cortex in which activity decreased with luminance level, transitions to higher luminance levels resulted in positive slopes, whereas transitions to lower luminance levels resulted in negative slopes. With no effect of light history, the trend observed when moving across slope values for step-up transitions (cyan line) is expected to be opposite from that of step-down transitions (gray line). The actual observed trend for step-down transitions is depicted (cyan line). The angular difference between the observed and expected trends for step-down transitions serves as a proxy for the strength of the effect of prior light history. Sample size, L1 → L2: n = 81, L1 → L3: n = 56, L1 → L4: n = 79, L2 → L1: n = 78, L3 → L1: n = 84, L4 → L1: n = 68.

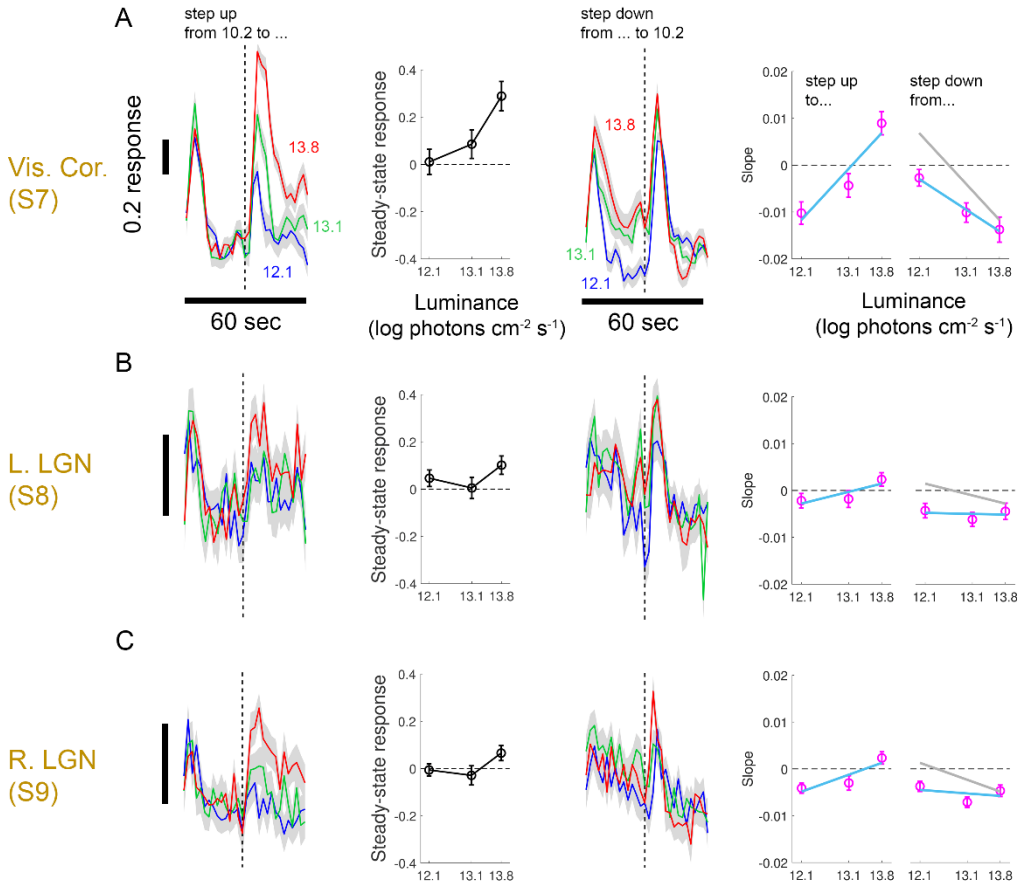
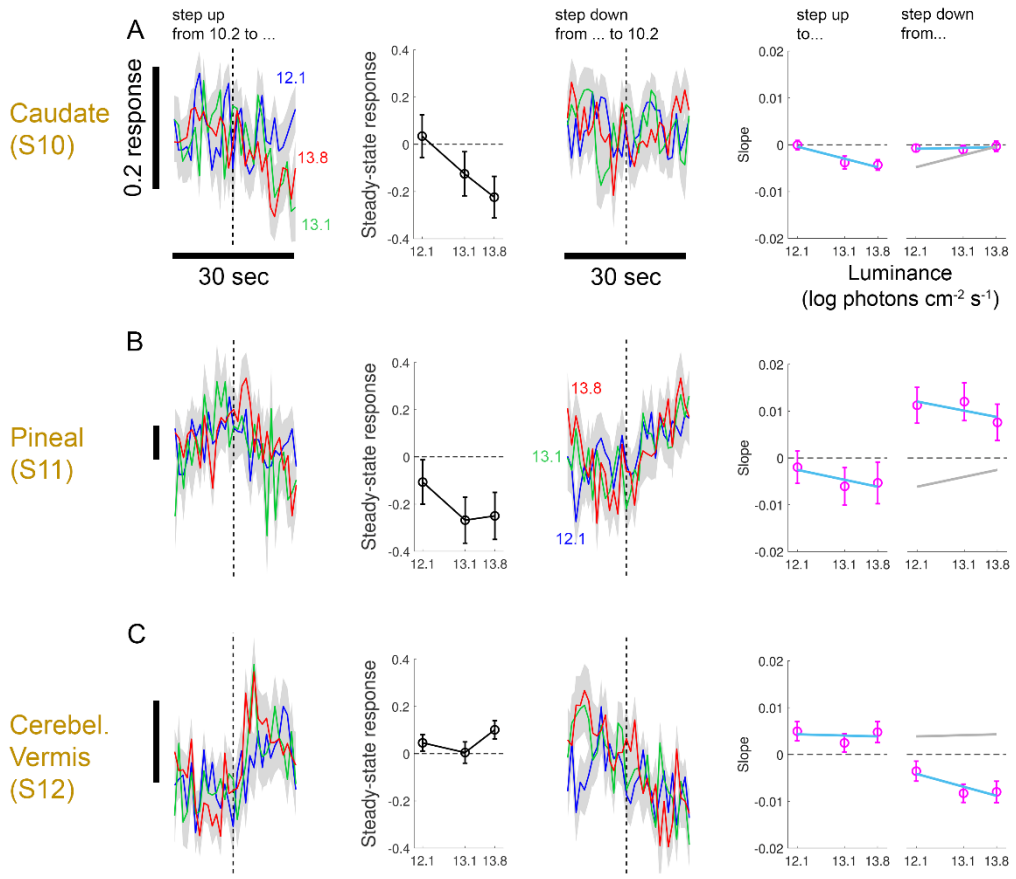


Figure 4. Light enhances activity along the thalamo-visuocortical pathway

Conventions as in Figs. 4. (A-C, two leftmost columns). Steady-state activity monotonically increased with increasing luminance level in all three luxotonic regions along the thalamo-visuocortical pathway. Vertical bar representing 0.2 BOLD response in (A) applies for all panels (A-C). In visual cortex (A) and LGN (B,C) in which activity increased with luminance level, transitions to higher luminance levels resulted in zero or negative slopes, whereas transitions to lower luminance levels resulted in zero or positive slopes. Sample size, L1 → L2: n = 81, L1 → L3: n = 56, L1 → L4: n = 79, L2 → L1: n = 78, L3 → L1: n = 84, L4 → L1: n = 68.



Supplementary Figure 2. Light monotonically varies activity in the pineal, caudate and cerebellar vermis

Conventions as in Figs. 3 and 4.

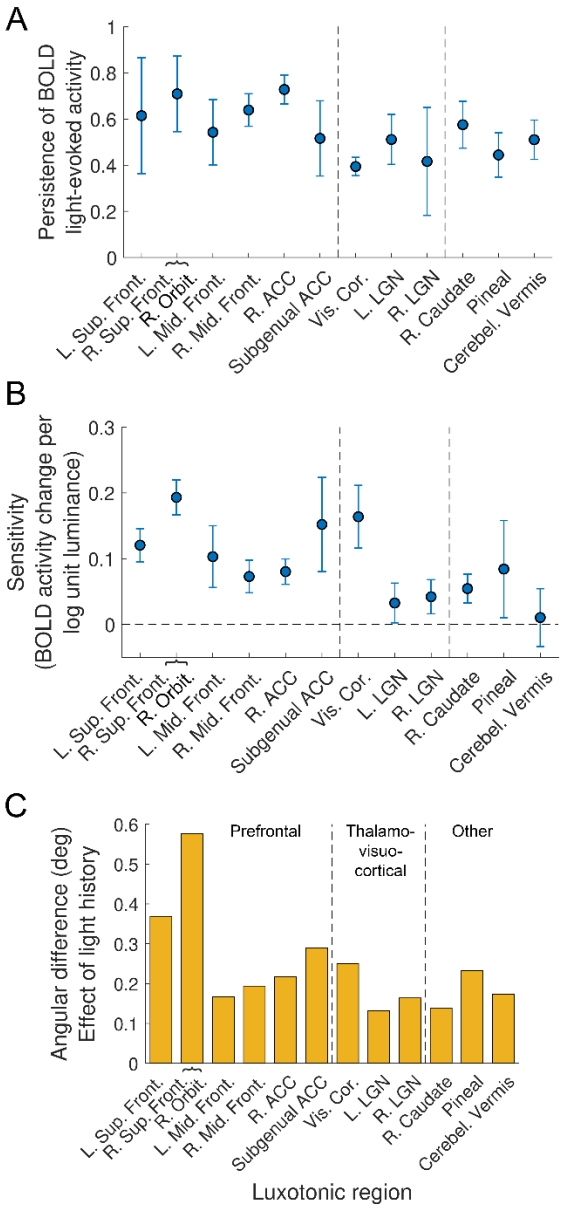


Figure 5. Effect of prior light exposure on brain activity is largest in the prefrontal cortex

Persistence (A) and sensitivity (B) in the identified luxotonic regions. (C) Strength of the effect of light history estimated as the angular difference between the observed and expected trends for step-down transitions. While prior light exposure affected all luxotonic regions, the effect on the left and right superior frontal gyri and right orbital gyrus was largest.

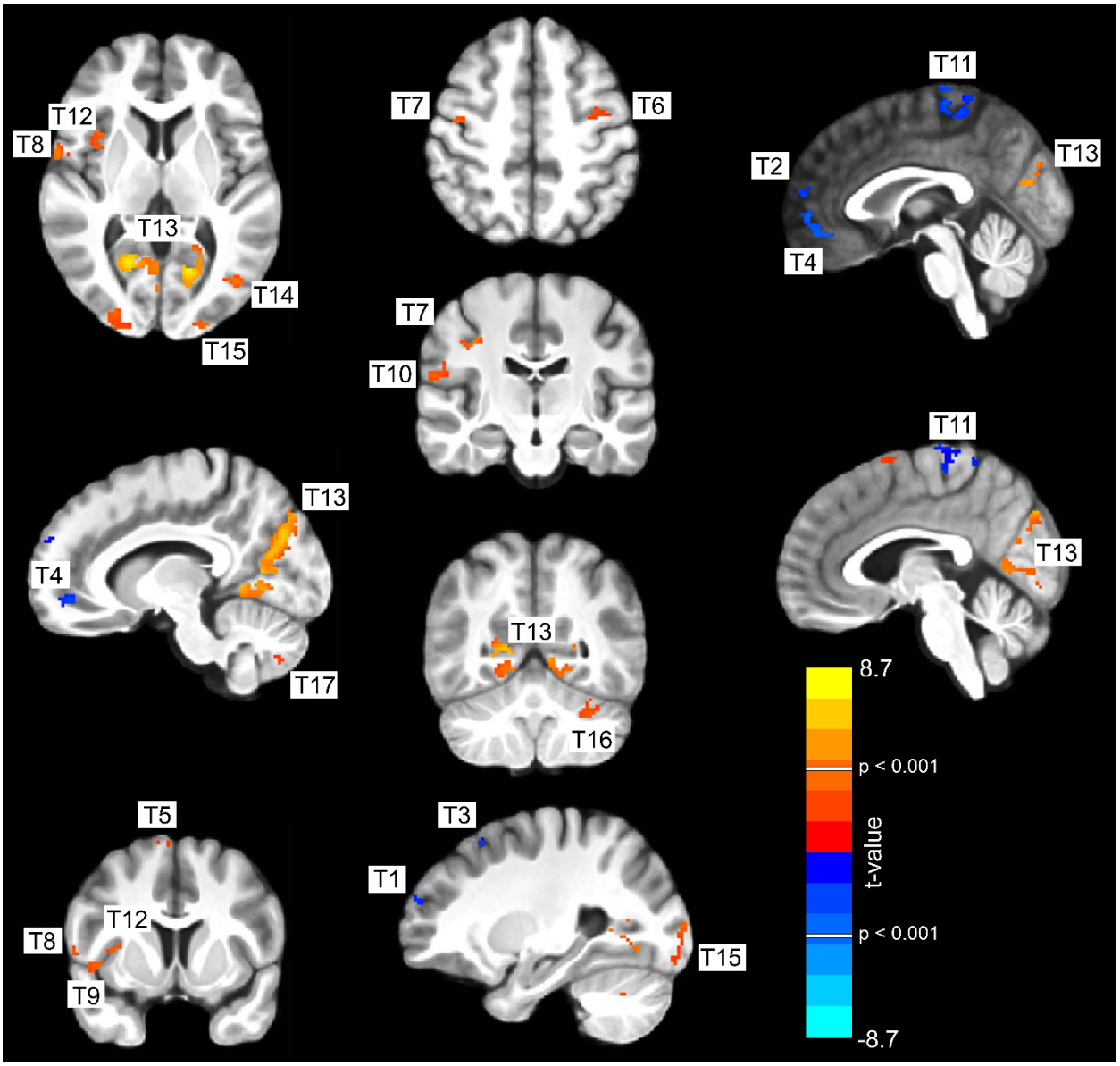


Figure 6. Cortical, subcortical, and cerebellar luxotonic regions that show a significant transient component

The 17 identified luxotonic regions color-coded based on the contrast for monotonic increases or decreases as a function of luminance level. Color scale corresponds to t-value: warm colors (positive t-values) – light-evoked responses increases with luminance level; cool colors (negative t-values) – light-evoked responses decreases with luminance level. Color bar, t-values ranges ±8.7, and images are thresholded at $p < 0.001$, t(two-tailed) = 3.621 (white horizontal lines). Anatomical underlay represents the mean of all 20 subjects following spatial alignment. Regions: T1, L. Super. Medial Front.; T2, R. Super. Medial Front.; T3, L. Mid. Front.; T4, L. ACC; T5, R. Suppl. Motor Area; T6, L. Precentral; T7, R. Precentral; T8, R. Front. Oper.; T9, R. Front. Oper.; T10, R. Parietal Oper.; T11, Paracentral Lob.; T12, R. Insula; T13, Vis. Cor.; T14, L. Mid. Occip.; T15, L. Inf. Occip.; T16, L. Cerebel.; T17, L. Cerebel.

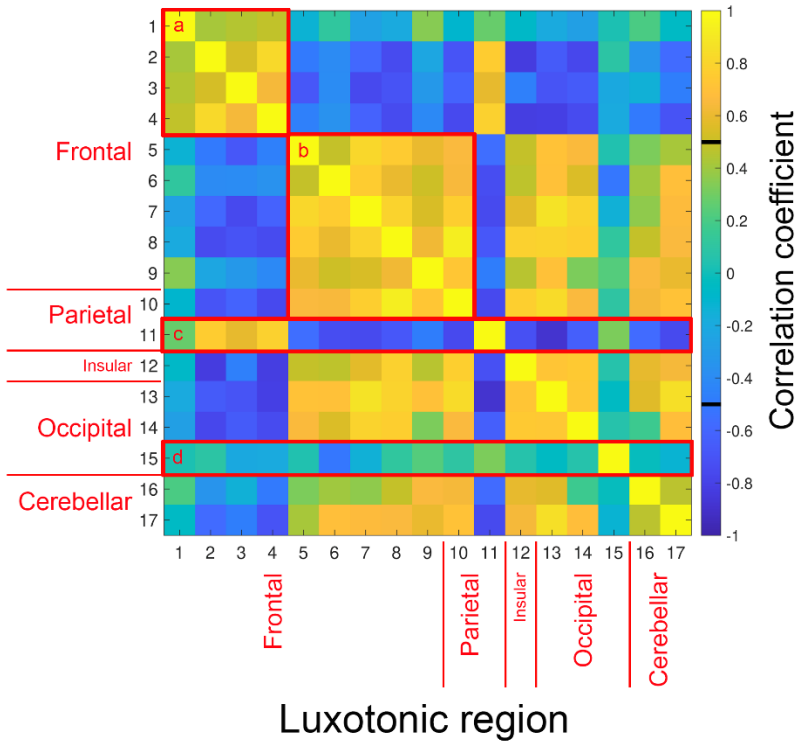
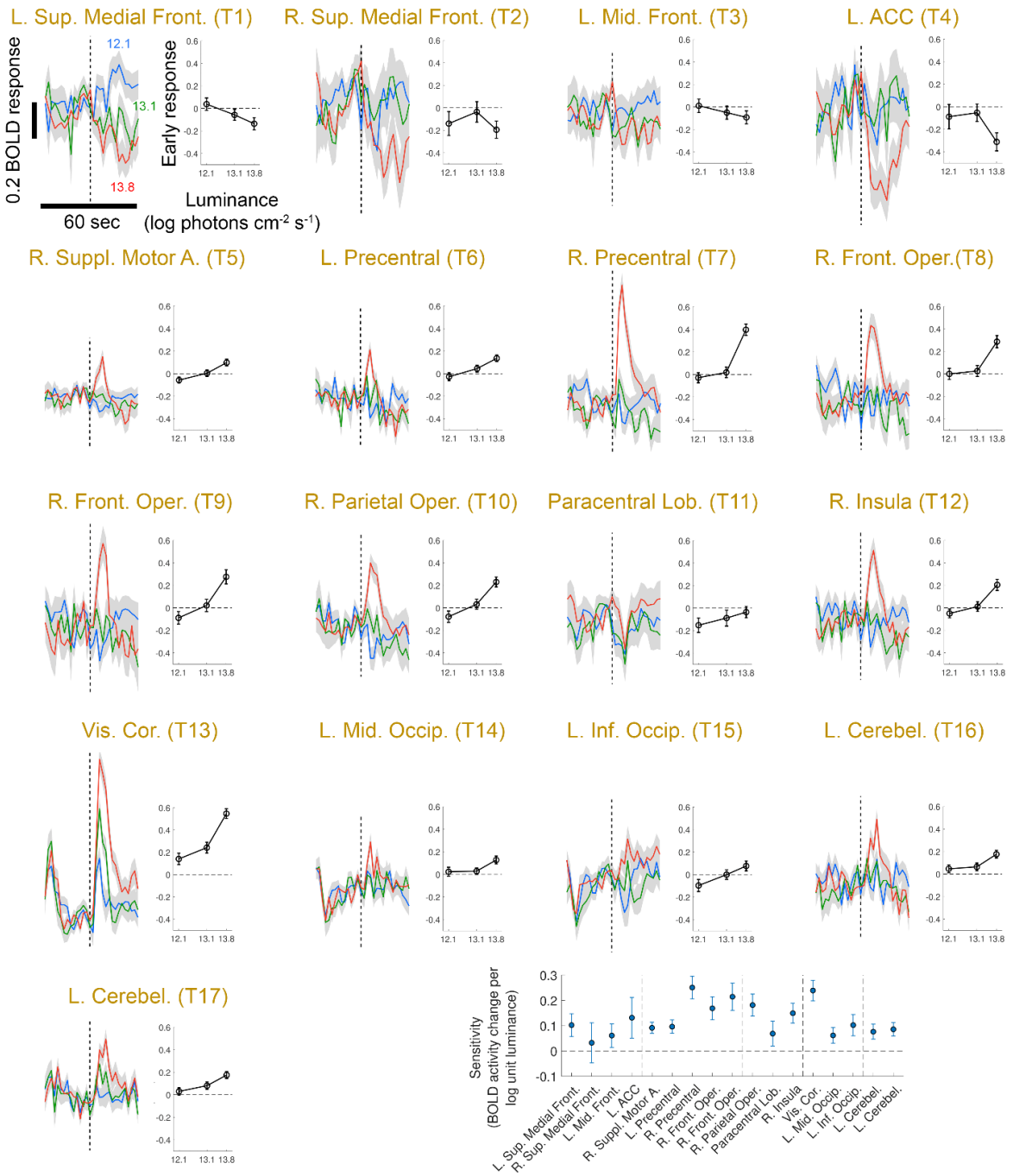


Figure 7. Pair-wise functional connectivity between identified luxotonic regions with a transient component.

Pair-wise Pearson correlation between the 17 identified transient luxotonic regions. Regions are grouped as frontal, parietal, insular, occipital, and cerebellar. Identity of luxotonic brain regions is given in Fig. 6. Correlation coefficient of ±0.51 corresponds to a significance level of 0.05 (indicated on the color scale bar).



Supplementary Figure 3. Light transiently modulates early cortical and cerebellar activity

(Left) BOLD Light-evoked responses to step up transitions – transitions in which luminance was stepped up from the same, lowest, luminance level (L1, 10.2 log photons cm^{-2} s^{-1}). Responses around individual transitions are depicted in different colors. Shaded gray areas represent the standard error from the mean. Dashed vertical line marks the transition time. (Second column from left). Early prefrontal activity monotonically decreased with increasing luminance level (regions T1-T4) while early activity in all other regions (T5-T17) increased with luminance level. Vertical bar representing 0.2 BOLD response applies to all panels. (Bottom right) Sensitivity of the transient response in the identified luxotonic regions. Sample size, L1 → L2: n = 81, L1 → L3: n = 56, L1 → L4: n = 79.

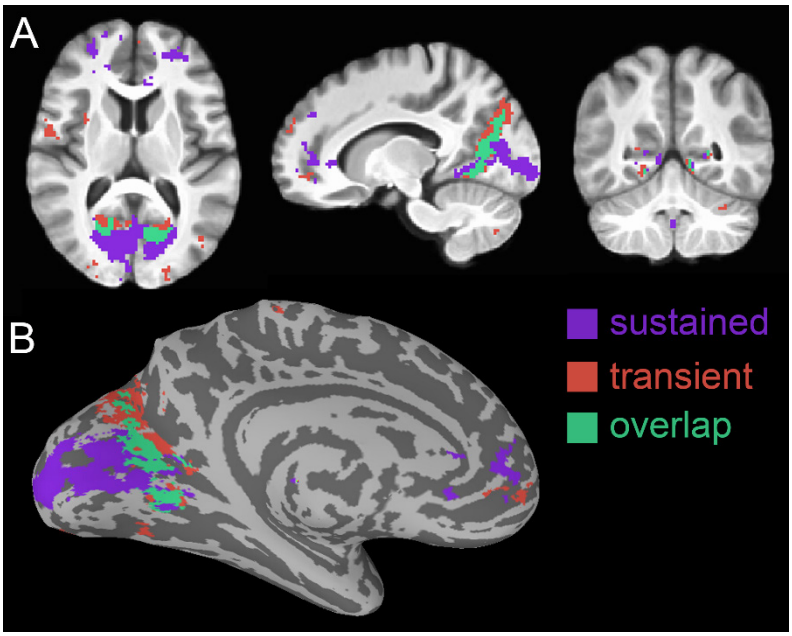


Figure 8. Sustained and transient response regions overlapped along the parieto-occipital sulcus

(A) Horizontal, mid sagittal and coronal sections showing the overlap between luxotonic regions in which activity showed both significant sustained and transient components. Sustained and transient regions are marked in purple and red, respectively, and overlapping areas are marked in green. (B) Same data presented on an inflated brain model.