Alerting effects of daytime light exposure – a proposed link between light exposure and brain mechanisms

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The effects of light on alertness have been shown several times and the proposed cause has been suppressed melatonin levels. The relation of melatonin and alertness applies at night but not by day when there is hardly any melatonin. Still, light can be used to improve daytime alertness, but how? This paper describes the brain mechanisms involved in light-induced daytime alertness and proposes a novel model of two parallel mechanisms. In addition to the well-established circadian pathway, it is suggested that light can use the amygdala in the limbic system to send signals to the cerebral cortex. The participation of the amygdala in light-induced alertness means that light is provoking and modulating emotions that induce alerting responses. The model is assembled from known relations but has not yet been verified as a functional system. The paper proposes methods to test the model.

1. Introduction

Melatonin is a sleep-inducing hormone produced in the brain by the pineal gland. There is evidence that exposure to short wavelength light in late evening induces melatonin suppression resulting in greater alertness in the middle of the night when melatonin secretion is peaking.¹ This is explained by the fact that the secretion of melatonin is controlled by the suprachiasmatic nucleus (SCN), the brain’s pacemaker responsible for generating circadian rhythms in mammals. The SCN on the other hand, takes input from the retina via a photic pathway called the retinohypothalamic tract (RHT).

However, the fact that the link between melatonin and alertness applies only at night but not by day when there is hardly any melatonin, is often ignored. In fact, much previous work has focused on the neurologic basis for the alerting effects of light exposure at night, but little is understood regarding the mechanisms responsible for the alerting effects of light during daytime. Yet, results show that light can be used to improve daytime alertness.²,³ The question is, how?

Over the past decades, research on the relation of light exposure to daytime alertness has concentrated on effects instead of causes.⁴,⁵ Only a few studies have attempted to examine the mechanisms underlying light-induced daytime alertness.³ This explains why there is a lot of inconsistent data on the role of light in alertness during wakefulness. It also explains why it has not been possible to find a consensus on the parameters of light, such as the illuminance, spectrum, duration and timing of light exposure, that induce the greatest changes in alertness. The authors claim that these problems could be overcome if the brain mechanisms and projections behind the alerting effects of light were
to be more thoroughly investigated and discussed.

Animal studies done in the 1970s have shown that there is a direct visual input from the retina to the limbic system, also known as the centre of emotions. This suggests that light cues may affect emotional behaviour.6 Furthermore, it has been shown that the limbic and preoptic systems project to brain areas that play key roles in the arousal system, such as the lateral hypothalamus (LHA), orexin neurons and the locus coeruleus (LC).7,8 These neural connections from retina via the limbic system to the arousal system exist but they have never been discussed from a light-induced alertness point of view.

This paper combines known relations on the theoretical level and proposes a tentative and hypothetical model of two parallel mechanisms that allow light to affect alertness in daytime. It suggests that in addition to the circadian pathway, the alerting effects of light can be based on light cues that travel to the amygdala and further to the arousal system. This novel model has not been verified as a functional system, but the paper does suggest some experiments that could be used to confirm the proposed mechanism.

This paper first describes the neurotransmitters and receptors that make up the two branches of the ascending reticular activating system. After that the projections from the retina to the brain areas promoting arousal and sleep will be discussed on the basis of these projections a model of two parallel pathways for the light stimulus to induce alertness is proposed. In the central role is the amygdala that provides a limbic pathway alternative to the SCN and the circadian pathway. The amygdala is known to perform a primary role in the processing and memory of emotional reactions. Hence, if the amygdala is involved in light-induced alertness, it means that alertness can result from an emotional stimulus caused or modulated by the light. Therefore, the relationship of light, emotion and alertness is discussed more thoroughly. Finally, practical suggestions on how to test the hypothetical model are given.

2. The ascending reticular activating system

Alertness is based on stimuli travelling from the brainstem through the thalamus, hypothalamus and basal forebrain to the cerebral cortex.9,10 This activation system, also known as the ‘ascending reticular activating system’, is located in the reticular formation in the core of the brainstem near the junction of the pons and the midbrain (Figure 1). There are many neurons in the reticular formation, the midbrain and the hypothalamus that play an essential role in that the regulation of alertness. The most important of them are the noradrenergic, histaminergic, dopaminergic, serotonergic and cholinergic neurons located in the locus coeruleus (LC), tubermammillary nucleus (TMN), ventral tegmental area (VTA), dorsal raphe nucleus (DR) and laterodorsal and pedunculopontine tegmental area (LDT/PPT), respectively.11 These nuclei have many afferents and efferents and they are also connected to each other. Their involvement in alertness is described briefly in Table 1.

As shown in Figure 1, the activation system contains two branches along which the reticular neurons sends projections to the cerebral cortex. The first branch, the dorsal one, innervates the thalamus by projections originating in the two cholinergic structures – the LDT/PPT nuclei. The second branch, the ventral one, projects into the lateral hypothalamic area (LHA), basal forebrain and the cerebral cortex from the monoaminergic LC, DR, VTA and TMN pathways. These projections promote arousal. For a more detailed review of the activation system and its branches see reference 9.
3. Connections from the retina to brain regions promoting alertness

Figure 2 shows the most essential connections from the retina to the brain regions that are involved in promoting alertness.

The SCN, located in the hypothalamus, is the brain’s master clock\(^{13}\) that coordinates the circadian rhythms based on light input from the outside world during daytime and by melatonin secretion during night time.\(^{14}\) Photic information is transmitted to the SCN directly along the RHT from the melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs) located in retina.\(^{15}\) Although the ipRGCs are sufficient for photic entrainment, recent findings have shown that the classical rod and cone photoreceptors also contribute in the photic entrainment of circadian rhythms.\(^{16}\)

In humans, the SCN also seems to receive indirect input from the retinoreceptive intergeniculate leaflet (IGL) via the geniculo-hypothalamic tract (GHT).\(^{17,18}\) There is, however, contradictory literature on whether the retinal afferents to the IGL are from the melanopsin expressing ipRGCs\(^{19}\) or from the classical photoreceptors.\(^{20}\) The SCN projects to many brain structures involved in arousal regulation.\(^{21}\)

Orexin is a neuropeptide produced in the hypothalamus.\(^{22}\) It has been suggested that neurons containing orexin increase arousal by innervating with the nuclei that take part in activation between the autonomic nervous system and the cerebral cortex.\(^{23,24}\) Among

\(^{13}\) Saper et al., 2012

\(^{14}\) Saper et al., 2012

\(^{15}\) Saper et al., 2012

\(^{16}\) Saper et al., 2012

\(^{17}\) Saper et al., 2012

\(^{18}\) Saper et al., 2012

\(^{19}\) Saper et al., 2012

\(^{20}\) Saper et al., 2012

\(^{21}\) Saper et al., 2012

\(^{22}\) Saper et al., 2012

\(^{23}\) Saper et al., 2012

\(^{24}\) Saper et al., 2012
Table 1 A summary of the nuclei of the ascending reticular activating system and their involvement in alertness

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Abbreviation</th>
<th>Location</th>
<th>Neurotransmitter</th>
<th>Role in alertness</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locus coeruleus</td>
<td>LC</td>
<td>Brainstem</td>
<td>Noradrenaline</td>
<td>Enables the body to perform well in stressful situations by secreting noradrenaline to the cortex</td>
<td>Aston-Jones et al.,70 Samuels and Szabadi80 and Aston-Jones81</td>
</tr>
<tr>
<td>Dorsal raphe nucleus</td>
<td>DR</td>
<td>Brainstem</td>
<td>Serotonin</td>
<td>Creates a calming or an arousing effect depending on where in the brain serotonin is secreted</td>
<td>Jacobs and Azmitia82</td>
</tr>
<tr>
<td>Laterodorsal tegmental area</td>
<td>LDT</td>
<td>Brainstem</td>
<td>Acetylcholine</td>
<td>Modulates sustained attention and mediates alerting responses together with the PPT</td>
<td>Jacobs and Azmitia82</td>
</tr>
<tr>
<td>Pedunculopontine tegmental area</td>
<td>PPT</td>
<td>Brainstem</td>
<td>Acetylcholine</td>
<td>Modulates sustained attention and mediates alerting responses together with the LDT</td>
<td>Jacobs and Azmitia82</td>
</tr>
<tr>
<td>Ventral tegmental area</td>
<td>VTA</td>
<td>Midbrain</td>
<td>Dopamine</td>
<td>Increases vigilance as well as secretion of many other hormones by secreting dopamine</td>
<td>Oades and Halliday83</td>
</tr>
<tr>
<td>Ventrolateral preoptic nucleus</td>
<td>VLPO</td>
<td>Hypothalamus</td>
<td>Galanin and GABA</td>
<td>Blocks the arousal system by efferents containing gamma-aminobutyric acid (GABA) and galanin</td>
<td>Saper et al.,12 and Gaus et al.38</td>
</tr>
<tr>
<td>Tuberomammillary nucleus</td>
<td>TMN</td>
<td>Hypothalamus</td>
<td>Histamine</td>
<td>Supports maintenance of cortical activation and wakefulness by secreting histamine</td>
<td>Parmentier et al.84</td>
</tr>
</tbody>
</table>
others, Saper et al.\textsuperscript{11} and de Lecea et al.\textsuperscript{22} state that the LHA is involved in the ascending arousal system and that loss of the orexin neurons in the LHA results in narcolepsy. Conversely, Harris and Aston-Jones\textsuperscript{25} have recently proposed that orexin neurons located in perifornical and dorsomedial hypothalamic areas increase arousal, whereas those located in the LHA would primarily be involved in reward processing.

The LHA innervates the orexin receptors of the LC\textsuperscript{26,24} as well as other nuclei in the ascending activation system.\textsuperscript{27–29} Serotonin and noradrenaline neurons in the DR and LC also send inhibitory feedback to the orexin neurons in the LHA.\textsuperscript{30} As shown in Figure 2, cholinergic and monoaminergic nuclei also project to each other.\textsuperscript{31,32} The amygdala is a subcortical structure of the limbic system, the centre of emotions. The neurons of the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{ipRGCs project to the SCN directly via the RHT\textsuperscript{15} and indirectly via the IGL and the GHT.\textsuperscript{17,18} Also rods and cones are likely to take part in these projections.\textsuperscript{16,19,20} In addition, the IGL receives input from the LC,\textsuperscript{67} DR,\textsuperscript{68} and TMN\textsuperscript{69} (these projections are not present in this figure). The SCN projects indirectly to the LC using the ventral subparaventricular zone (vSPZ), the dorsomedial nucleus of the hypothalamus and the LHA as relays.\textsuperscript{30,31} The SCN also projects to the VTA using the medial preoptic nucleus as a major intermediary.\textsuperscript{71} The LHA contains orexin peptides\textsuperscript{72,73} that innervate the orexin-1 receptors (OX1R) and/or orexin-2 receptors OX2R\textsuperscript{74} in the LC,\textsuperscript{26} DR,\textsuperscript{27} TMN\textsuperscript{28} and LDT.\textsuperscript{29} The DR and LC also send inhibitory feedback to the LHA.\textsuperscript{30} The LC and DR have reciprocal connections.\textsuperscript{31} The VTA excites the LC.\textsuperscript{75} The PPT and the LDT are both excited and inhibited by the LC and PPT and LDT\textsuperscript{76} project back to the LC.\textsuperscript{77} The TMN inhibits noradrenaline release in the LC.\textsuperscript{27} In contrast to other hypothalamic nuclei, the LC does not project reciprocally to the TMN.\textsuperscript{78} In addition to the SCN and the vSPZ,\textsuperscript{30} the ipRGCs also project directly to the amygdala.\textsuperscript{30} The amygdala sends limbic inputs including the CRF neurons to the orexin neurons in the LHA\textsuperscript{33,34} as well as to the LC.\textsuperscript{35,78} The VLPO promotes sleep by inhibiting the LHA, TMN, LC and DR\textsuperscript{12}. Note that the majority of the connections have been found while testing rodents or monkeys.}
\end{figure}
amygdala containing corticotrophin-releasing factor (CRF) stimulate the orexin neurons in the LHA and activate the LC contributing to maintenance of arousal. The amygdala gets significant projections from the ipRGCs but projections from rods and cones are also possible.

During sleep, neurons of the ventrolateral preoptic nucleus (VLPO) block the arousal system by efferents containing gamma-aminobutyric acid (GABA) and galanin. The interaction between the VLPO branches is mutually inhibiting, and it has been said to work like an ‘on-off’ switch.

4. Circadian and limbic pathways in light-induced alertness

On the basis of the neurologic connections reviewed in the previous section, the authors propose a model of two separate major paths from retina to the activation system and then on to the cerebral cortex. The model is presented in Figure 3. The first path is formed by the RHT in the non-image-forming visual system. When this path is used, the light stimulus enters the ipRGCs in the retina and travels via the RHT or GHT giving input to the SCN and further to the circadian system. The involvement of rods and cones in the circadian pattern is also possible. This path is from now on referred to as the circadian pathway.

The second path starts from the retina, but instead of continuing directly or indirectly to the SCN, it continues to the amygdala, a limbic structure involved in many brain functions, including emotion. The fact that light of shorter wavelength has been found to elicit a stronger effect on emotional responses than longer wavelengths indicates that the photoreceptors involved in this pathway are ipRGCs and not rods and cones. It also means that the visual system in question is non-image-forming. However, the involvement of the classical photoreceptors cannot be ruled out. It is possible that part of the emotional response is related to the image-forming visual system and that light stimulates the classical photoreceptors in the same way as other visual stimuli. This path is from now referred to as the limbic pathway.

As shown in Figure 2, the amygdala and the SCN both use orexin neurons in the LHA to deliver messages to the LC, the core of the activation system. Therefore, the authors suggest that the different paths are parallel to each other and that they unite in orexin.
neurons continuing on the same path to the activation system (Figure 3). Light’s ability to affect alertness via melatonin suppression is well established\(^{40-43}\) and it has been used to explain the changes in alertness during nighttime light exposure. Therefore, the circadian pathway can be considered a known pathway for light-induced alertness. The limbic pathway, on the other hand, has never before been considered as the mechanism behind the alerting effects of light although the theory is in accordance with the findings of Vandewalle et al\(^{20}\) who report that light can modulate emotional processing by the amygdala. The theory is also consistent with Figueiro et al.\(^{44,45}\) who recently conducted a series of studies with long-wavelength, red light and short-wavelength, blue light and reported that more than one mechanism, not just the melatonin pathway, must be involved in light-induced alertness.

There is also recent evidence that these two proposed pathways work at the same time and influence one another. In mice, disturbances of limbic system have been found to affect the circadian system\(^{46}\) and vice versa.\(^{47}\)

It should be noted that some neural connections presented in Figure 2 have been characterised in only a few mammalian species, primarily nocturnal rodents and not diurnal mammals.\(^{48}\) Therefore, in future studies, it should be ensured that the circadian and limbic pathways as described in Section 4 are present in humans. If they are, they could explain why it is so hard to reach consensus on the parameters of light, in terms to the timing and duration of exposure, light spectrum, colour temperature and light level that produce the greatest responses in alertness.\(^{1,2,5,20,49,85-87}\)

5. Relationship of light, emotions, and alertness

If the limbic system, and more precisely the amygdala, is involved in light-induced alertness, it means that alertness can result from an emotional stimulus caused or modulated by the light. Hence, the alerting response depends strongly on what kind of emotions the light induces. The hypothetical model opens two questions. First, how can it be verified and second, what is the relationship of light, alertness and emotion. This section will discuss what is currently known about the relationship of light, alertness and emotion. In Section 6 suggestions on how to test the model will be presented.

Brain imaging studies show that emotions and arousal are connected and that functional brain differences are associated with stimulus arousal.\(^{50}\) Activation of the visual cortex is greater when people are exposed to emotional as compared to neutral stimuli.\(^{50}\) In skin conductance measurements, unpleasant stimuli have been shown to increase electrodermal activity more than pleasant stimuli. Interestingly, women show a bias towards more activation for unpleasant than for pleasant stimuli and men show a tendency in the opposite direction.\(^{51}\) On the assumption that the alerting response depends on the pleasantness of the stimulus, it is important to consider what makes a light stimulus pleasant or unpleasant.

The psychology of colour has been widely studied\(^{52}\) and it is well known that colour elicits positive or negative feelings and emotions.\(^{53,54}\) For instance, the colour red has been associated with excitement, yellow with cheerfulness and blue with comfort and security.\(^{55}\) In a study of college students, a blue colour was found to elicit both negative and positive feelings;\(^{56}\) positive, because blue was associated with the ocean and relaxing, calming effects, and negative, because blue was also associated with night and depression. This means that colours can provoke either type of feeling and that the alerting response depends on the emotions that it provokes. However, it also means that caution should be taken when asserting...
relationships between specific colours and emotional states because it is subject to large individual and even cultural differences in response.

Because colour is clearly connected to emotions, the same can be expected to apply to the colour of light. In fact, in psychophysical tests colour of light has been shown to relate to the pleasantness and activating effects of light. In a workplace study conducted in 2008, blue-enriched white light was found to improve subjective measures of alertness and positive mood compared to normal white light. In a laboratory study conducted in 2010, both red and blue lights reduced sleepiness and improved momentary mood. These results indicate that light can directly affect mood and alertness and that the spectral composition of the light plays a role in these effects.

The parameters of light in the investigations of the relationship of light, emotions and alertness are highly interesting to lighting researchers. So far the studies have concentrated on the impact of colour or the combination of colour and intensity of light on emotions, and the impact of the duration and timings of the light exposure on emotions still remain largely unknown. To be able to develop a broad understanding of the physiological mechanisms behind the relationship Plitnick et al. suggest that the light stimulus should be defined independent as its apparent colour.

It is important to distinguish between the direct or indirect effects of light on emotions and hence on alertness, because that allows using light in different applications. A direct effect is when light itself is able to induce emotion, such as a sunny sky that makes a person happy. An indirect effect is caused by light or lighting that modulates the response to another stimulus and therefore indirectly affects the mood and alertness. This is the case in theatre lighting.

Recently, Vandewalle et al. investigated the indirect effects of the light spectrum in the presence of vocal stimuli and demonstrated the acute influence of light on emotional brain processing. The next step would be to study whether light has direct effects on emotions by excluding all other stimuli in laboratory conditions. Knowledge of the direct effects could be used in different light treatment applications to acutely enhance alertness by light. Indirect effects of ambient light could be applied to working places and other environments where there is need to modulate the mood to retain a good level of alertness.

6. Proposal for how to test the model

As reported by Phan et al., the amygdala has a specialised role in processing visual emotional stimuli compared to auditory or recall stimuli. Passive viewing, hence emotional visual stimuli without any cognitive task, activates the amygdala. However, it has been suggested that the visual stimulus has to be strong to create a conscious emotion. If the emotional stimulus is too brief or too weak the amygdala might not process it and direct it to conscious thinking. Therefore a wide range of irradiance values should be used to achieve a broad understanding on the relationship of light and emotions.

It seems that both classical and non-classical photoreceptors contribute to non-image-forming responses in rodents. Lall et al. have suggested that low and high irradiances of light activate different retinal photoreceptors. At low scotopic light levels (irradiance of 10⁷ photons/cm²/s at 500 nm) rods play a dominant role probably signaling solely via the visual pathway. At moderate light levels (irradiance of 10¹² photons/cm²/s at 500 nm) both rods and cones give input to non-image-forming vision. There is recent evidence that under dark-adapted conditions cones dominate these responses but that light adaptation limits their influence. Although these photopic irradiances are within the
sensitivity range of cones it seems that their involvement in non-image-forming vision can mainly be seen after abrupt changes in irradiance. Therefore, currently undefined rod pathways are considered to play the key role in these circumstances. Melanopsin in the ipRGCs seems to encode high irradiances (irradiance of $10^{15}$ photons/cm$^2$/s at 500 nm$^{43}$) and drive responses in most daylight conditions.

To test the suggested model and see whether light can evoke emotions that induce alertness, the following three-step study protocol is proposed.

In the first step, the subjects are exposed to different light stimuli as well as darkness and they are asked to rate their mood on the Visual Analogue Mood Scale (VAMS)$^{64}$ in the absence of any other stimuli or tasks. The purpose of the first step is to simply investigate how the light stimuli affect the emotional state. Using the same light stimuli in the second step allows the comparison of the results.

The second step consists of four subtests with darkness as a baseline as illustrated in Figure 4. The first two subtests are done at scotopic lighting levels with blue and red light as the stimuli, and the following two at photopic lighting levels with blue and red light, respectively. Mesopic lighting levels are included in the third step.

In the third step, the study protocol is advanced by four more subtests to investigate the gradient change from photopic to scotopic light level during the 4-minute light exposure and vice versa with both blue and red light. This simulates the change in lighting conditions at dusk and dawn, respectively, and is needed to test whether such changes...
intensify the emotional and alerting effects of light stimuli.

Each subtest in steps 2 and 3 is recorded using functional Magnetic Resonance Imaging (fMRI) scanning sessions over the baselines and the light exposure. Self-ratings of sleepiness and emotion are measured verbally throughout the recording at 1-minute intervals. Sleepiness is measured with the Karolinska Sleepiness Scale (KSS) and emotion with a shortened version of the Profile of Mood States (POMS). Mood state is used as an indicator of emotion because measuring emotional reaction is complex.

From the fMRI scans the activation and the deactivation of the amygdala, the SCN and the LC are analysed as a function of time. The activation patterns will reveal whether there is any order of activation and therefore a causal relationship between the light-induced activation of the amygdala or the LC and the increase in experienced levels of emotions or alertness; whether the amygdala and the SCN are activated simultaneously or in turns depending on the light stimulus; and whether different light stimuli induce non-image-forming responses that outlast the exposure and decline slowly, or classical image-forming responses that cease very shortly after the stimulation.

It is hypothesised that the activation and the deactivation patterns induced by photopic and scotopic light stimuli will differ from each other. Also, it is hypothesised that the activation and the deactivation depend on the spectral composition of the stimuli. However, it is not possible to predict which stimuli will activate the amygdala, the SCN and the LC the most, because not enough is yet known about the projections from the three photoreceptors to the brain areas in question.

7. Conclusions and perspectives

The direct link from the retina to the limbic system was identified in the 1970s creating the basis for understanding how light cues may affect alertness. This paper is the first to suggest that the limbic pathway for light-induced alertness operates in parallel with the well-established circadian pathway. According to this novel theory the visual light stimulus can travel via the RHT in the circadian system or use the limbic system, the centre of emotions, to create an emotional response to the light cue. The paper suggests that the two pathways unite in orexin neurons and continue as the same path to the arousal-promoting nuclei.

The existence of the limbic pathway for light-induced alertness would mean that the alerting effects of light can depend on what kind of emotions the light induces or modulates. For example, a person can become more alert in daylight compared to darkness because he is either happy (pleasant direct stimulus), or because the light exposure is disruptive (unpleasant direct stimulus), or because the light has an influence on how he feels about his view (indirect effect on external emotional stimulus).

The theory of a second pathway is substantial, because it extends knowledge of the mechanisms behind the alerting effects of light and gives a possible explanation as to how light affects alertness during daytime where there is hardly any melatonin. To verify the theoretical model, it is essential to study the relationship of light, emotions, circadian processes and alertness. The fact that people have very individual reactions to light complicates the design of scientific tests and the interpretation of the results. Therefore, it is challenging to find appropriate objective methods to study emotions and alertness. Some methods to test the novel model are, however, suggested.

An open question is whether these two proposed systems, the circadian and the limbic, work simultaneous or alternatively. More research is needed to see how these two systems influence one another. The involvement
of an emotional factor in the circadian processes could explain why people show such different responses in tests concerning light-induced alertness.

This paper is expected to be of great interest to both lighting and brain researchers because if the model is verified, it can reveal the missing link between the light exposure and the enhancement of brain responses driving daytime alertness. Therefore, it has the potential to set the basis for future studies.

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