Dispatches

Circadian Photoreception: Spotlight on the Brain

In addition to its visual function, the mammalian eye detects light for a range of behavioral and physiological responses that are separate and apart from sight. Recent studies have begun to shed light on the areas of the brain that respond to such 'non-visual' photoreception in the human eye.

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While the role of the mammalian eye in detecting light for vision has long been known, it has only recently emerged that the eye performs a dual role in detecting light for a range of behavioral and physiological responses that are distinct from sight. In humans, ocular light exposure resets circadian rhythms, induces suppression of the nocturnal pineal hormone melatonin, induces pupillary constriction, increases heart rate, enhances subjective ratings of alertness, and changes the frequency of electroencephalogram (EEG) brain waves that are indicative of a more alert state [1–5]. These effects of light are collectively termed 'non-visual' or 'non-image forming' responses and are sometimes grouped under the term 'circadian photoreception', as much of the behavioral and neuroanatomical work that first identified these effects was focused on studies of the ability of light to shift the timing of the endogenous circadian (near-24 hour) pacemaker. While our basic understanding of this photoreceptor system has been derived largely from tracing and gene knockout experiments in rodents, Maquet and colleagues [6] have made the first step in attempting to identify non-visual brain areas in humans that show enhanced activity to light using functional magnetic resonance imaging (fMRI).

The rapid advances in understanding how light stimulates non-visual functions were led by the discovery of a novel opsin termed melanopsin in the mammalian eye [7]. Melanopsin is a G-protein-coupled receptor with seven transmembrane domains that phylogenetically resembles invertebrate opsins more closely than it does other mammalian opsins, indicating that it may have evolved before the vertebrates. Surprisingly, melanopsin protein was found to be located, not in the outer retina where rhodopsin and cone opsins are present, but in about 1–3% of cells in the ganglion cell layer, spread across the retina in a network-like distribution. These melanopsin-containing ganglion cells project to multiple brain areas involved in non-image forming responses, including the suprachiasmatic nuclei (SCN) of the hypothalamus, the site of the principal mammalian circadian pacemaker [8] (Figure 1).

Remarkably, the melanopsin-containing ganglion cells are directly photosensitive, with a peak spectral sensitivity to short-wavelength blue light (λ_{max} = 482–484 nm) [9,10], closely matching the peak sensitivity for non-image-forming responses to light, including circadian phase resetting, melatonin suppression and pupillary constriction, but differing significantly from the absorption spectra of rods and cone photopigments. Moreover, when melanopsin is expressed in cells that are normally light-insensitive, it confers photosensitivity to those cells with short-wavelength sensitivity [11]. Genetic deletion of melanopsin attenuates, but does not abolish, non-image forming responses to light, while rodless, coneless animals retain normal non-visual responses to light. Melanopsin-deficient animals with disrupted phototransduction in the rods and cones, however, are totally insensitive to light [12].

In parallel with the early rodent experiments, clinical studies showed that some totally blind humans, lacking any detectable visual response to light, retained normal non-visual function in terms of their light-induced melatonin suppression [13] and circadian phase resetting responses [14]. Similarly, red–green color blind patients show normal melatonin suppression during white and green light exposure [15]. Action spectra for melatonin suppression in normal subjects indicated short-wavelength sensitivity, with a λ_{max} ~460 nm [2,16], close to that for melanopsin cells and rodent behavioral responses, and again not matching the action spectra for human scotopic or photopic vision, or absorption spectra for the individual short, medium and long wavelength-sensitive cone photopigments. We can categorically state, therefore, that there exists a novel non-rod, non-cone photopigment in the mammalian eye that preferentially mediates non-visual responses to light. How can we make use of this information in the real world, however?

In addition to its role in synchronizing circadian rhythms, light has a direct alerting effect on the human brain, which makes intuitive sense for a daytime-active species. The pathways by which light acutely induces arousal are not known, however. In their new work, published recently in *Current Biology*, Maquet and colleagues [6] examined brain activation during an auditory performance test, before and after exposure to bright white light during the daytime. Brain areas associated with performance of the auditory task showed enhanced responses following exposure to light, suggesting increased alertness at the neuroanatomical level. In addition, the light-induced

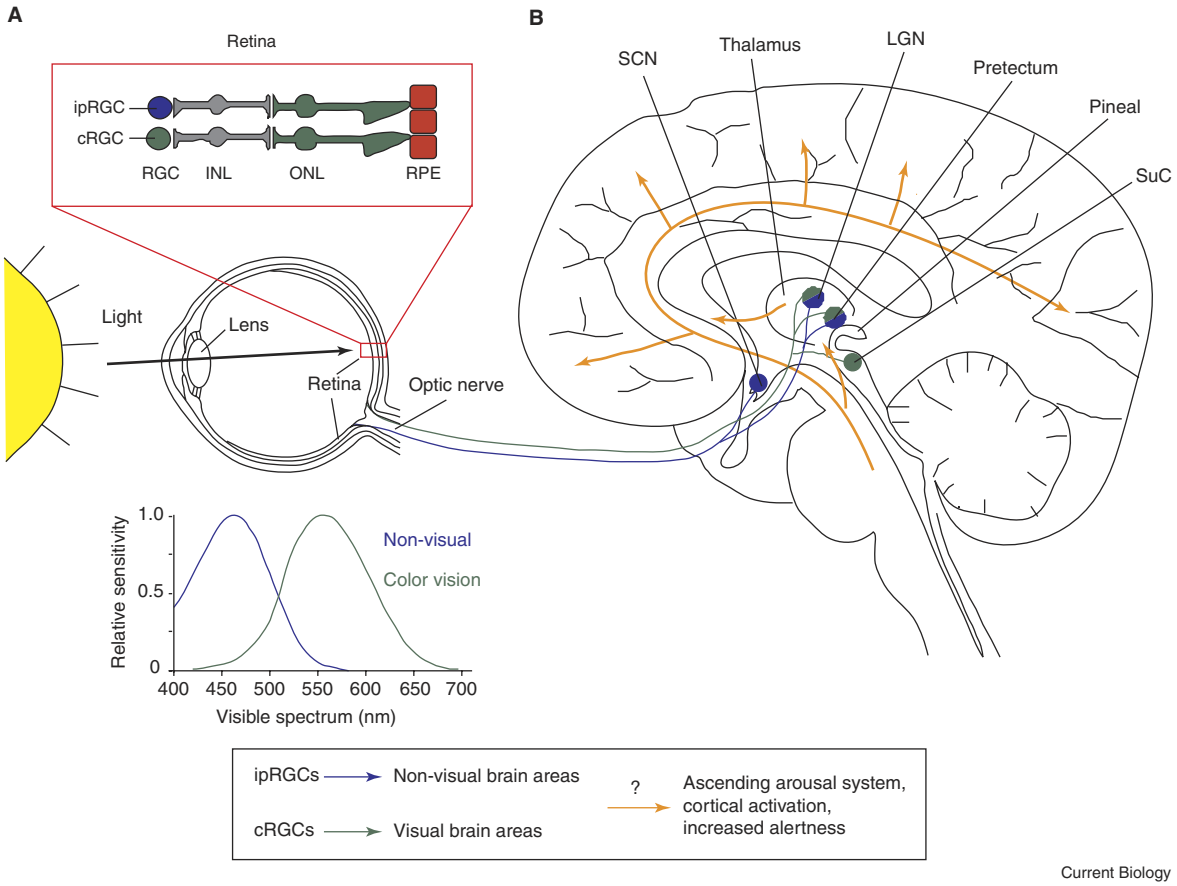

Figure 1. Pathways for light-induced activation of non-visual brain areas.

(A) Light exposure activates melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGC), which are most sensitive to short-wavelength visible light, and cone-driven classical ganglion cells (cRGC) of the color vision system, which are most sensitive to mid-wavelength light (λ_{max} = 555 nm). (B) Melanopsin-containing ipRGCs project to a range of 'non-visual' areas of the brain, including the suprachiasmatic nuclei (SCN), which then project multisynaptically to the pineal gland, as well as to many areas that share input from the visual photoreceptor system, such as the lateral geniculate nucleus (LGN), pretectum and superior colliculus (SuC). Through as yet unidentified pathways, light stimulates the ascending arousal system and eventually the cortex to enhance alertness and cognition. INL, inner nuclear layer; ONL, outer nuclear layer; RPE, retinal pigment epithelium. (Adapted from [20].)

increase in subjective alertness corresponded with enhanced responses in the posterior thalamus, including the pulvinar nucleus, which has been implicated in visual pattern discrimination and visual attention [17]. While this new study [6] did not address the spectral sensitivity of these responses, the data are consistent with the time course of light-induced cell firing patterns in melanopsin-containing intrinsically photosensitive retinal ganglion cells [9,10] in that light-induced activation occurred as soon as the light was turned on, but persisted for minutes after the light was turned off.

The question remains, however, which pathways in the brain mediate light-induced activation of cortical activity associated with increased alertness and attention. The intrinsically photosensitive retinal ganglion cells and classical retinal ganglion cells — both of which receive input from rods and cones — send widespread projections to the brain, including the hypothalamus, thalamus, pretectal area and superior colliculus. Each retino-recipient brain nucleus, in turn, projects differentially to subcortical and cortical brain areas involved in a myriad of behavioral and physiological functions. Determining the pathways by which light acutely activates the ascending arousal system, stimulates cortical activity, and enhances vigilance and cognitive performance remains an important, yet formidable task.

One mechanism by which light could exert its alerting effect is through the activation of neurons in the SCN, the site of the circadian pacemaker. The SCN strictly controls the timing of release of the pineal hormone melatonin, the rhythm of which is closely associated with the endogenous sleep propensity rhythm. Light exposure at night acutely suppresses melatonin and induces a simultaneous increase in alertness. It is not known, however, whether light increases alertness by suppressing the sleep-promoting action of melatonin, or if these physiological responses to light occur independently. Notably, suppression of melatonin by light does not account for light-induced arousal in the

daytime [6,18] when melatonin is undetectable.

Preliminary studies measuring light-induced changes in EEG correlates of arousal have shown that blue light (460 nm) is more effective than green light (555 nm) at suppressing delta/theta activity (0.5–5 Hz), which is considered a marker of both the circadian and homeostatic drive for arousal. Furthermore, blue light preferentially activates high-alpha frequency oscillations (9.5–10.5 Hz) [5], which closely parallel the circadian rhythm of melatonin production [19]. It may be possible that different arousal responses have differing spectral sensitivities to light, theoretically mediated through differing relative contributions of the short-wavelength sensitive melanopsin-driven system and the longer-wavelength sensitive photopic and scotopic visual photoreceptor systems. Action spectra for the alerting effects of light on multiple EEG frequencies during both day-time and night-time exposures would address this question, and if combined with the simultaneous creation of action spectra for fMRI responses, would create a very powerful technique to establish the photobiological and neurobiological pathways through which light alerts the brain. We, along with many who wish to use light as a fatigue countermeasure in clinical, military and occupational settings, await these results with great interest.

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Behavioural Ecology: Promiscuous Fathers Sire Young that Recognize True Family

Most theories of kin selection assume that animals are able to distinguish relatives from non-relatives. This is especially difficult in situations where mixed parentage precludes that relatedness is recognised by familiarity. Recent work shows that, within the same brood, young bluegill sunfish that are fathered by cuckolders — but not those sired by parental males — pick out their relatives using self-referent phenotype matching and not familiarity.

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The theory of kin selection revolutionised our understanding of animal sociality by demonstrating that an individual can gain genetic benefits by helping both its own progeny and/or a non-descendent kin [1]. Accordingly, individuals can increase their inclusive fitness disproportionally, as by helping relatives they pass more copies of their own genes on to the next generation. But can individuals