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Vision: Melanopsin as a *Raumgeber*

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Two new studies show that neural systems receiving inputs from the melanopsin-containing retinal ganglion cells encode spatial information and therefore see the world in more detail than previously thought.

The mammalian eye sees with specialized photoreceptors: the cones, which provide for form, color and motion in daylight; and the rods, which provide for night vision. But light also influences physiology and behaviour beyond sight, for example, entraining our biological clock to the Earth's 24-h rotation and light–dark cycle. This function is mediated by the blue-sensitive photopigment melanopsin, discovered only 20 years ago [1]. Two new studies in mice reported in a recent issue of *Current Biology* reveal that the melanopsin cells of the retina provide more detail than previously thought to the brain areas involved in the perception of images [2] and setting of circadian rhythms [3].

Intrinsically photosensitive retinal ganglion cells (ipRGCs) express the melanopsin photopigment and have large receptive fields, integrating information over space. Because ipRGCs respond to light in a slow and sustained fashion — continuing to fire after a light is turned off — they integrate light over time, creating an ideal system to encode changes in overall light intensity (irradiance). While small in number, the ipRGCs project broadly within the brain (Figure 1A). The suprachiasmatic nucleus (SCN), which serves as the circadian pacemaker in mammals, receives ipRGC input. The ipRGCs also project to the dorsolateral geniculate nucleus (dLGN), the first stop on the route to conscious cortical vision, where the role of melanopsin signals has been less clear. While dLGN neurons respond to melanopsin-only contrast [4], there has been little expectation that the slow, sparse ipRGCs contribute to spatial vision.

In marked contrast to this standard understanding, however, the two new studies demonstrate that the melanopsin system is capable of encoding images. Mouland and colleagues [3] find a population of SCN neurons sensitive to spatial structure, providing a detailed representation of visual space. Further, Allen and colleagues [2] demonstrate that a population of dLGN neurons respond to spatial contrast seen exclusively by melanopsin. Both remarkable findings complement each other in demonstrating a novel role for melanopsin in encoding spatial contrast.

By way of the SCN, light acts as a *zeitgeber*: a signal that aids in synchronizing the internal biological clock to the external illumination. Previous studies [5–7] found that neurons in the SCN preferentially respond to light filling the entire visual field, encoding overall light intensity to track the natural light–dark cycle given by solar illumination. In contrast, Mouland and colleagues [3] find that around 75% of SCN neurons respond to spatial patterns, suggesting the circadian pacemaker has access to the spatial structure of light: a *raumgeber*. By

presenting images to mice while recording electrical activity from the SCN, they found that some neurons have a center-surround organization, as stimuli hitting the center of the receptive field cause an increase in firing while stimuli hitting the surround of the receptive field cause inhibition (Figure 1B).

Allen and colleagues [2] provide a complementary finding within the dLGN. Around 20% of dLGN neurons respond to melanopsin stimulation, and all of these modulate their firing by the spatial position of the melanopic contrast. One puzzling aspect of these neurons is that they have only an excitatory center with no inhibitory surround that would sharpen the encoding of spots presented to the center of the receptive field (Figure 1C).

The cells responding to melanopic contrast prefer a slow temporal regime, slower than the cells that respond to cone and rod stimuli. Melanopsin is not ideal, therefore, to encode a fast change in visual input such as that elicited by eye or head movements. Instead, spatial melanopic contrast provides a representation of the visual environment. By simulating the effect of eye and head movements on melanopsin signals within natural images, Allen and colleagues [2] find that the ipRGCs could extract stable features of the environment at low temporal and spatial frequencies. This might help track features of the visual environment that are relatively invariant to head and eye movements, such as the difference in brightness above and below the horizon.

The extent of the visual field spanned by the melanopsin-responsive units in dLGN is around 13 degrees, well within the 6–17 degree range of the receptive field diameters of ipRGCs in the retina [8–10]. This suggests that post-retinal responses to spatial contrast defined by melanopsin activation is inherited from the retina. In the SCN, more complex processing must be at work to account for the center-surround antagonism, as the subclass of M1 ipRGCs that dominate retinal inputs to the SCN do not have an inhibitory surround. The SCN may perform some local computation, in which the projections of different RGCs are differenced, or perhaps the classic (non-melanopsin) RGCs give rise to the spatial sensitivity seen in SCN.

Mouland and colleagues [3] also address whether the ability to encode

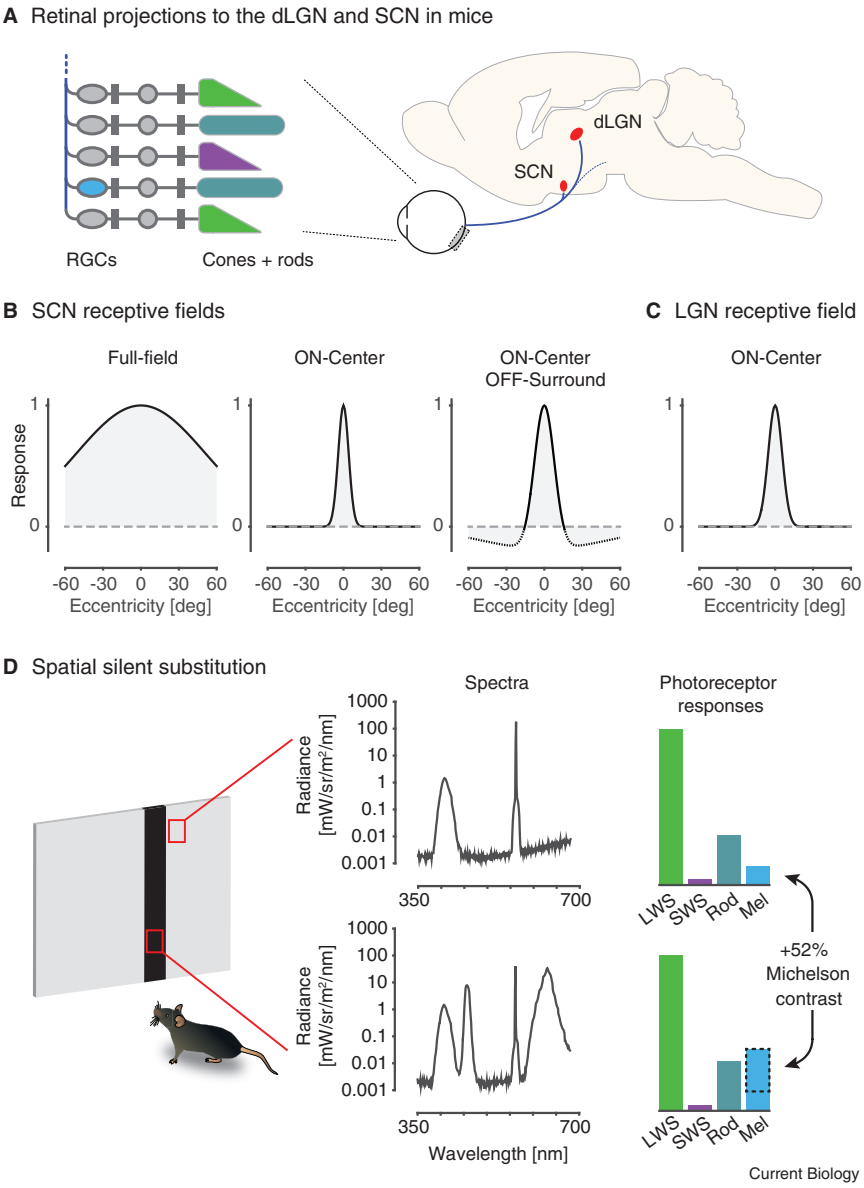

Figure 1. Melanopsin provides a spatial image to the brain.
(A) Schematic representation of the retina and its photoreceptors, and the subsequent projection of the retina to the dorsolateral geniculate nucleus (dLGN) and the suprachiasmatic nucleus (SCN) (adapted from [18]). A subset of retinal ganglion cells (RGCs) contain the photopigment melanopsin, indicated in cyan. (B) Schematic representation of the receptive fields of SCN neurons. (C) Schematic representation of the receptive fields of dLGN neurons. (D) Method of silent substitution. *Left*: Cartoon depiction of the stimulus display with vertical bars. *Center*: Spectral content of the images at the two locations highlighted. *Right*: Activation of the different photopigments by the different spectra.

spatial images is of functional importance to circadian photoentrainment. By comparing the effect upon circadian phase of an environment with diffuse illumination versus one with vertical bars, they find that there is no additional phase shift from spatial contrast. Functionally, the circadian output is therefore determined by overall illuminance.

More generally, it is still to be seen if these spatial signals from the ipRGCs have behavioral consequences. For example, if there is no effect of spatial patterns on circadian phase, why would SCN neurons encode spatial detail? Perhaps spatial contrast simply arises from the available retinal signals. As there are no retinal neurons that cover the entire visual field, spatial sensitivity is just

inherited from the finite receptive field sizes in the retina. This passive-transfer explanation, however, would not account for the center-surround responses within the SCN, which seem to require an active computational process (as the M1 ipRGCs lack an inhibitory surround) and some maintenance of retinotopic organization. There are examples of a functional role for a circadian spatial signal. The position of the sun may be a weak *zeitgeber* for birds living in continuous light in the Arctic [11], although this cue could in principle also be carried by the classic RGCs or extraocular photoreceptors.

A challenge to the idea of a sharply defined spatial receptive field for melanopsin-mediated function is that melanopsin is expressed not just in the soma and dendrites, but in the axons running in the nerve fiber layer in rodents [12] and primates [13]. This would lead to the possibility that stimulation of the axons could trigger spatially non-selective responses. Consistent with this possibility, blue light stimulation of the optic disc (the physiological blind spot) elicits pupil constriction presumably mediated by melanopsin expressed within the nerve fiber layer [14].

Cone signals encoding high spatial frequency information are carried by both the classic RGCs, and by the ipRGCs in which they are integrated with the intrinsic photosensitive signal from melanopsin. Because the spectral sensitivities of the cones and melanopsin are overlapping, it is very difficult to tease apart the relative contributions of these photoreceptors. To overcome this, Allen and colleagues [2] used a clever, 'silent-substitution' spatial stimulus in their measurement of dLGN responses. Pairs of lights were tailored such that the effective photon catches for the light coming from different points on a screen are matched for cones and rods, but not for melanopsin. The resulting visual stimuli contained images of bars that were invisible to the rods and cones but could only be seen by melanopsin (Figure 1D).

In their study of SCN inputs, Mouland and colleagues [3] employed a different strategy, using fast-flickering stimuli biased to elicit responses from cones. Almost all retinal projections to the SCN are M1 (~80%) and M2 (~20%) ipRGCs, so it seems likely that the ability to code spatial contrast in the SCN is from cone signals via the ipRGCs. However, a tiny fraction (<1%) of retinohypothalamic projections are not melanopsin-expressing and perhaps arise from classic RGCs [15]. Furthermore, the SCN receives indirect signals from the LGN. More work is required to determine the origin of spatial coding in the SCN. In principle, the spatial silent substitution paradigm could be adapted to create selective stimuli for the study of the photoreceptor contributions to the SCN, but this was not reported here.

Melanopsin is often described as supporting 'non-image-forming vision', in contrast to the spatial images provided by the rods and cones. The work of Mouland, Allen and their colleagues calls for a revision of this dichotomy. There is plenty of spatial detail conveyed by the melanopsin-containing retinal ganglion cells, endowing neural structures the ability to represent melanopic images.

In people, the possibility that spatial patterns have an effect on circadian photoreception remains an intriguing venue for future research. Our perception of space is modulated by after-effects that are specific to spatial frequency and are the source of numerous visual illusions that can trick our conscious perception (e.g. [16]). The presence of spatial coding within the SCN raises the possibility of 'circadian visual illusions'. Are there spatial configurations that produce a circadian phase shift larger than for a diffuse light? A similar effect has been found for flashes, in which a train of short flashes induces a larger circadian phase shift than a continuous light of the same intensity [17]. Perhaps a combination of temporal and spatial contrast could provide the ultimate circadian *trompe-l'œil*.

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