A Thalamic Circuit Lights up Mood

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The contributions of areas downstream of retinal ganglion cells involved in the processing and regulation of mood remain largely unspecified. In this issue of *Cell*, Fernandez et al. (2018) identify a thalamic circuit within the perihabenular region (pHb) linking daily changes of light pattern to mood regulation.

Life on earth has evolved in the context of a 24-hr light-dark cycle, with early organisms developing internal metabolic rhythms that exploited daily variations in food and oxygen availability. In multicellular organisms, *circadian* rhythms (from latin, circa dieum, "about a day") are seen across all tissues and are known to be critical for immune, musculoskeletal, cardiac, and neural function (Hastings et al., 2007). In mammals, where light patterns constitute the chief circadian *zeitgeber* (German for "time giver"), the retina is the sole transducer of light (Hattar et al., 2003). A remarkable series of studies in the early 2000s identified melanopsin-containing intrinsically photoactive retinal ganglion cells (ipRGCs) as specific transducers of the circadian light signals (Hattar et al., 2002). By projecting directly to the body's master circadian clock, the suprachiasmatic nucleus (SCN), ipRGCs can influence a wide range of photo-biological functions independent of visual processing (Hattar et al., 2003).

Among many such functions is the process by which light patterns influence mood and affective states. In humans, abrupt changes in light patterns are known to trigger manic episodes, and seasonal variations of the light-dark cycle are associated with depressive episodes (Bedrosian and Nelson, 2017). As such, understanding the biological underpinnings of how light patterns influence mood is of paramount importance, particularly given the ever-increasing aberrant light exposure through mobile electronic devices. A critical role for the ipRGC system in mediating the impact of light on mood has been shown by an earlier study in which mice exposed to an aberrant light cycle (a 7-hr cycle [T7] instead of a 24-hr cycle [T24]) develop depressive endophenotypes only when ipRGCs are intact (LeGates et al., 2012). However, because light exposure changes sleep-wake patterns through the SCN, it had been unclear whether such affective regulation was part of a broader circadian process dependent on the ipRGC-SCN pathway or was independently processed through one of the many ipRGC non-SCN brain targets (LeGates et al., 2012). In this issue of *Cell*, Fernandez et al. (2018) use a variety of approaches, including ablation of ipRGCs that project to non-SCN targets, to show that a thalamic circuit within the perihabenular region (pHb) mediates the impact of light on mood.

The authors capitalize on their ability to selectively ablate non-SCN-targeting ipRGCs based on their expression of both melanopsin (Opn4) and *Brn3b*. Specifically, by crossing Opn4-Cre$^{+/-}$ with Brn3b^{DTA} mice, diphtheria toxin (DTA) selectively ablates non-SCN targeting ipRGCs. This manipulation does not impact activity rhythms or their changes in response to a T7 cycle. It also does not alter the negative impact T7 light patterns have on spatial learning tests or their neural correlates in hippocampal slices. Together, these data suggest that the SCN is, indeed, sufficient for maintaining a normal circadian rhythm under T7 despite mediating its negative impact on learning.

The surprising result came when studying the affective changes associated with the T7 cycle. Mice in which the non-SCN targeting ipRGCs were ablated are resistant to the known depressive impact of T7 seen in WT control mice, including the sucrose preference test as a measure of anhedonia and the tail suspension and/or forced swim tests as measures of learned helplessness. The fact that an intact SCN circuit is not sufficient to transduce light patterns to mood changes suggests another ipRGC target, and a few clues make the perihabenular (pHb) region a likely candidate. First, this region shows robust cFos induction following light pulses; and second, T7 blunts its rhythmic expression of the PER2 clock gene in an ipRGC-dependent manner. This remarkable differential response to T7 and T24 is of interest because the SCN does not show it, making this pHb light-responsive circuit of potential interest.

This interest raises a tantalizing question: what type of circuit is this light-responsive pHb? Because the pHb sits at the border between the thalamus, a central regulator of forebrain activity (Schmitt et al., 2017), and epithalamus (habenula), it was critical to determine whether the light-responsive circuitry was thalamic or epithalamic. A comprehensive genetic, histological, and electrophysiological screen indicated that this putative circuit is indeed thalamic and projects to cortical (ventromedial prefrontal cortex; vmPFC) and subcortical (nucleus accumbens; NAcc) regions known to be important for affective control.

Further experiments provide compelling evidence for this thalamic circuit being the transducer of light patterns to affective states. *In vivo* monitoring of bulk activity measures using GCaMP6m-dependent fiber photometry confirmed that pHb thalamic neurons are indeed light-responsive. Intriguingly, the T7 cycle generates significantly higher and more frequent population activity peaks compared to the T24 cycle, suggesting

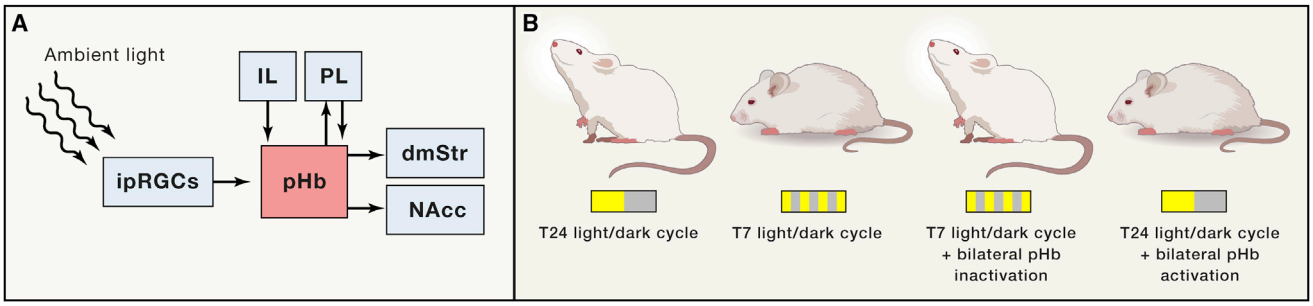

Figure 1. A Thalamic Circuit Linking Daily Changes of Light Pattern to Mood Regulation

(A) The pHb thalamic circuit. The perihabenular nucleus (pHb) receives light information from melanopsin-containing intrinsically photoactive retinal ganglion cells (ipRGCs). The pHb projects to and receives descending feedback from two areas in the prefrontal cortex, the prelimbic (PL) and infralimbic cortex (IL). Additionally, the pHb projects to other areas previously implicated in mood-related processing: the dorsomedial striatum (dmStr) and the nucleus accumbens (NAcc). (B) pHb mediates light's effect on mood. *From left to right:* Mice housed in a T24 cycle exhibit no significant mood-related deficits. In contrast, mice housed under a T7 cycle develop depressive symptoms. When housed under T7 cycles, TetX Cre-mice with bilateral pHb silencing through injections of AAV/Cre-GFP become robust to the depressive effects of T7 and are statistically indistinguishable from control T24 mice. Lastly, c-Fos^{CreERT2} mice with bilateral chronic activation of pHb housed under T24 develop depressive symptoms.

that more frequent light exposure result in some sort of population over-excitation. Could this over-excitation be a driver of mood alterations? The answer is likely yes because mimicking this process by selective activation of this pHb thalamic population using excitatory designer receptors exclusively activated by designer drugs (DREADDs) is sufficient to increase measures of anhedonia and learned helplessness, similar to the T7 cycle. Are pHb neurons necessary for the impact of light on mood? This answer is also likely yes because expressing tetanus toxin (TeTx) in these neurons diminishes the mood-altering effects of the T7 cycle. As such and through multiple lines of observational and causal experiments, compelling evidence indicates that a thalamic pHb circuit transduces light patterns into affective regulation (Figure 1).

The study by Fernandez et al. (2018) has far-reaching impact on both our basic understanding of brain function as well as potential translational applications. From a basic perspective, this study identifies a novel thalamic region that may play important roles in affective state control. Notably, this circuit does not appear to be broadly engaged in affective regulation but rather specialized in tracking light pattern changes. This type of specialized homeostatic regulation has been shown for other thalamic circuits, such as those within the paraventricular thalamus (PVT) in chronic stress (Penzo et al., 2015) and midline thalamic circuits in sleep-wake control (Gent et al., 2018). More generally, this is part of the broader perspective on the thalamus playing central roles in functional forebrain organization well beyond relaying signals in sensory processing (Rikhye et al., 2018). From a translational perspective, gaining circuit access to how light patterns translate into mood changes is of great value. It will now be possible to monitor the impact of changing light patterns on circuit activity, perhaps even using non-invasive neuroimaging in humans with seasonal affective disorders. Using single-cell genetic analysis in animals, it will also be possible to further examine neurons within these circuits and perhaps identify novel druggable targets for future interventions.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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