Drosophila simulans [4] show that there is far less skew in the non-recombining regions of the genome than expected (although there is still some relative to the standard neutral model's predictions). Simulations were carried out where the harmful mutations, whose input drives BGS, were made mainly recessive, with the heterozygote for the mutation only showing 20% of the mutation's homozygous effect (as opposed to 50% in the standard BGS model) and where individual mutations differed in the strength of their harmful effects [4]. It was found that for some parameter values, specifically when a proportion of mutations are weakly selected, relative to the reciprocal of the effective population size, AOD appears in no-recombination regions, increasing diversity and decreasing skew.

The key element in creating AOD is that the wild-type haplotype is lost (see Figure 1). Gilbert *et al.* [5] explore the conditions where this is likely, and find that loss of the wild-type haplotype is enhanced the more mutable loci there are. But selection must not be too strong, or the mutations are purged before they can reach high frequencies. Consideration of AOD thus indicates that there can be enhancements in genetic diversity in low recombination regions. Thus, Gilbert *et al.* [5] also looked at windows of the human genome, which included adjacent low-recombination and higher, medium-recombination regions, and looked at the levels of gene diversity to find cases where the low-recombination region had higher diversity. In this way, they identified 22 regions of the human genome as candidates for AOD. However, it remains uncertain whether these are cases of AOD or of true balancing selection, which leaves a similar signature in its effects on the SFS.

Clearly, with the avalanche of population genomic data from vast numbers of species, the search for AOD will be another role in which these new datasets can increasingly be used.

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Sensory Processing: Visual Sensitivity Gets High at Night

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Every day and night, the retina undergoes dramatic changes in its physiology and function. The prevailing view is that these daily changes affect the retinal output and thereby visual perception. Recent evidence suggests that modifications in higher-order processing centers, and not in retinal computations, account for variations in visual sensitivity.

The 24-h rotations of the Earth around its axis generate variations in most components of the physical world, such as ambient light and temperature. To ensure survival, animals have developed behavioral strategies to adapt to the constantly changing environment. Such strategies rely on a set of decisions necessary for organizing appropriate actions in response to environmental stimuli. In addition, endogenous timekeeping mechanisms such as circadian clocks provide the adaptive advantage of anticipating and preparing for the predictable changes. It is the interplay between circadian clocks and sensory processing of environmental stimuli that determines behavior at a specific time of the day [1].

The retina is a thin layer of light-sensitive brain tissue that lays in the

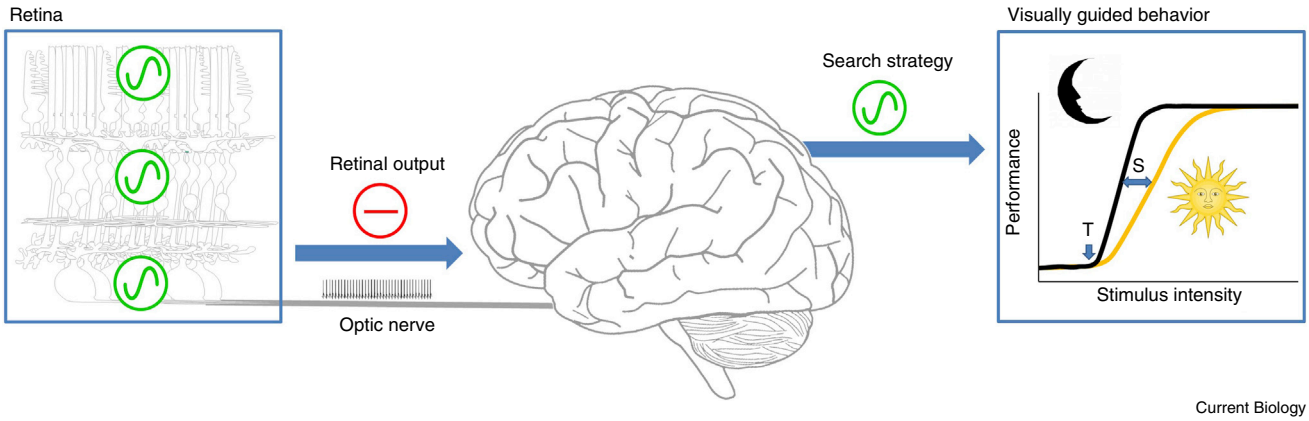

Figure 1. At the sensitivity limit of vision, daily changes in visual behavior performance rely on changes in the search strategy for visual cues and not on retinal rhythms.
The results by Koskela *et al.* [4] suggest that at the sensitivity limit of vision, retinal output does not change between day and night, even though retinal rhythms occur in every layer in the retina. Yet, mice change their behavioral strategy: they spend more time searching for visual cues at night. Thereby, mice increase their chances to make the correct choice at night. This results in an increase in visually guided behavior sensitivity (S) at night. Note that there is no day/night change in the behavioral threshold (T), which is constrained by the statistics of the stimulus and the sensitivity of alpha RGCs.

back of the eye. It has its own circadian clock and, not surprisingly, daily rhythms of physiology, through regulation of transcription, protein abundance, and function, have been reported in the retina [2,3]. It has long been assumed — although never thoroughly tested — that daily rhythms in the retina impact the retinal output and consequently visual perception. In a paper in this issue of *Current Biology* [4], a team led by Petri Ala-Laurila argues against this dogma. Using the mouse as a model, Koskela *et al.* [4] found that at light intensities close to the absolute visual threshold, there was no noticeable change in the retinal output between day and night. Yet, task-based visually guided behavior was found to be dramatically affected by the time of day, an event that the authors further linked to a shift in the efficacy of the search strategy for visual cues, which is controlled by high-level sensory areas in the brain. At the same time, the results question the functional relevance of retinal rhythms.

The experiments conducted by Koskela *et al.* [4] are remarkable because they were performed close to the sensitivity limit of vision. Dark-adapted mammals, including mice and humans, can detect a few photons that fall onto the retina [5]. Such sensitivity relies on a class of highly sensitive retinal photoreceptors (the rods) that can respond to single photons, and retinal circuits that balance noise rejection and single-photon signal retention. The dim light signals eventually make their way to the retinal ganglion cells (RGCs) — the output neurons of the retina whose axons project to higher visual centers deeper in the brain. The most sensitive RGCs, namely the alpha type RGCs, have an absolute threshold in the dark between 0.001 and 0.01 effective isomerizations per rod per flash (R*/rod/flash); that is, when only one photon is absorbed and transmitted per thousands or hundreds of rods [5,6]. However, while the absolute threshold of alpha RGCs and of vision have been closely scrutinized, interactions between the two and the daily cycle have not been examined.

In the Koskela *et al.* paper [4], mice were subjected to a dim light detection task in a water maze in the dark. They were first trained to associate an escape ramp from the water with a bright light stimulus. Once the mice reached 80% or more correct choices, their performance was tested for stimuli at different light intensities. Psychometric functions were created from plotting the fraction of correct choices as a function of stimulus intensity. The authors report that the threshold of the psychometric function was not different between mice trained and tested during the day (day group) from those trained and tested at night (night group) as the two curves both started to deviate from the chance level at around 0.01 R*/s. However, the shape of the function was dramatically different between the two groups. Specifically, the slope was much steeper for the night group and thereby the intensity needed for half-maximal performance was lower, consistent with an increase in sensitivity at night. Thus, whereas no change in threshold was noticed, behavioral sensitivity in light detection was higher at night compared to the daytime. Could the nighttime increase in visual behavioral performance reflect a change in retinal signal processing? By directly recording from RGCs in explanted neural retinas, the authors found that the threshold of the different types of alpha RGCs did not significantly change between day and night. The lack of daily variation in the retinal output strongly suggests that the observed changes in sensitivity of the behavioral task did not arise from the retina.

Koskela *et al.* [4] went a step further to consider where the daily change in visually guided behavior may originate from. With no change in the retinal output, the change must arise downstream of the retina. Accordingly, the authors speculated that the daily modulation in task performance might reflect changes in the efficiency of higher order sensory processing and/or

differences in the behavioral strategy used to sample visual space. To test the first possibility, they swapped the testing time. That is, mice from the night group were tested during the day whereas mice from the day group were tested at nighttime. Overall, it was found that the day group performed better when tested at nighttime, but surprisingly, the night group performance was as good as at nighttime when mice were tested during the daytime. Thus, behavioral performance was not directly associated with the time of the test, but rather with past history — the time of day at which mice were trained, a result that further excludes a role for retinal rhythms in the observed change in performance. Next, to determine if the difference in performance could originate from how the mice sample the visual space, Koskela *et al.* [4] developed a sophisticated technology to track and quantify twelve different features of the mouse head and body position, such as swimming time or the time the stimulus was in view. Every one of these features was found to be significantly different between day and night. Globally, mice spent more time at night sampling the stimulus, a strategy that most likely translates into an increase in the likelihood of making a correct choice.

Collectively, the core finding of the study by Koskela *et al.* [4] is the demonstration that daily changes in sensitivity of visually guided behavior at threshold reflect for the most part changes in the activity of higher order sensory processing centers and in the strategy to sample the visual space (Figure 1). Future work will determine the anatomical structures involved in the control of this behavior and address the intriguing irreversible nature of the change in strategy in the swap experiment. But the results from the study leave open the important question of the functional significance of circadian rhythms in the retina. So, despite the daily fluctuations in retinal physiology and function that are supported by a large body of literature [2,3], the retinal output near threshold appears unaffected. Interestingly, their conclusion is consistent with previous work that reported that the threshold of the scotopic electroretinogram (ERG) does not change between day and night in dark-adapted mice [7,8]. However, with brighter stimuli, changes in the photopic ERG [7,8], direction selectivity processes [9], and contrast sensitivity [10] have been clearly linked to retinal rhythms. Therefore, retinal rhythms may be more important for the computation of more complex and/or brighter visual stimuli than for the detection of brief, dim flashes. Koskela *et al.*'s new data [4] do not exclude a significant contribution of the retinal rhythms in the processing of visual stimuli at intensities above the threshold, but they have established the importance of higher order processing in the control of visual sensitivity at threshold.

Another solid and important finding from Koskela *et al.* [4] is that the absolute threshold of neither the retinal output nor the visually guided behavior of the freely moving mouse changes between day and night. Retinal circuits undergo dramatic reconfiguration between day and night [2,3]. Among these plastic processes stands electrical coupling between photoreceptors [11]. The relevance of photoreceptor coupling at visual threshold has been puzzling, in particular for rods because coupling is expected to decrease the single photon response amplitude and thereby impair signal/noise filtering in the retinal circuit [5,12]. It has been calculated that rod coupling would reduce human dark-adapted sensitivity by 10% [13]. The results by Koskela *et al.* [4] suggest that this is not the case. Thus, Koskela *et al.*'s data [4] raise the intriguing possibility that the most sensitive rod pathway — the *primary* rod pathway — may be unaffected by the daily changes in functional circuitry of the retina. Clearly, we are still a long way from fully understanding visual adaptation, but the work of Koskela *et al.* [4] brings us closer to this goal.

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