Colors cast long shadows on brain activity

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Light reaching the retina of the eye enables us to form images of our environment. A much older evolutionary benefit of light, though only recognized as important for humans in the past half a century, is that its 24-h irradiance profile informs the biological clock of the brain. The brain exploits this nonimage-forming (NIF) information to optimally synchronize and prepare physiology and behavior to the environmental opportunities and hazards of that cycle with 24-h predictability. However, it has only been for the last decade that not only circadian NIF effects, but also acute NIF effects of light on the brain, have been appreciated. Acute NIF effects are supported by retinal projections to brain structures involved in the regulation of sleep, alertness, mood, and cognition (1). In PNAS, Chellappa et al. (2) underscore the relevance of these projections for human cognitive brain activity. The report importantly extends their previous functional MRI (fMRI) studies showing that light intensity modulates brain activation of people performing a cognitive task. Chellappa et al. now show that the effect of light on brain activity depends on the color spectrum of light people were exposed to more than an hour before. Thus, colors cast long shadows on future brain activity.

Slower than the Speed of Light

Chellappa et al. (2) assessed the effect of modulating light intensity on brain activation during a working-memory task three times in each volunteer. Eighty minutes before, the volunteers had been exposed to 10 min of monochromatic light: once blue (461 nm), once green (515 nm), and once orange (589 nm). The 70 min in-between color exposure and onset of the task were spent in complete darkness. Surprisingly, even after this long interval, the prior color exposure determined the effect of modulating light intensity on brain activation during the task. Compared with prior blue light exposure, prior orange boosted the effect of modulating light intensity on brain activation during a working-memory task in prefrontal cortical

areas involved in executive control; in the thalamic pulvinar nucleus involved in arousal and cognition regulation; and in the fusiform gyri, cerebellum, amygdala, and a subcortical area encompassing the substantia nigra. Whereas prior orange exposure boosted future light sensitivity, prior blue exposure attenuated future light sensitivity. Prior green exposure was in-between. Apparently, prior color exposure has an enduring effect on

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the sensitivity to light, somewhere along the pathway from the retina into the brain.

Possible Mechanisms for Photic Memory

Where along this pathway—and how—could this “photic memory” be implemented in the brain? Chellappa et al. (2) suggest that photic memory is implemented at the earliest stage of the pathway, in the retina. The authors propose involvement of melanopsin, an opsin that renders a part of the retinal ganglion cells (RGC) intrinsically photosensitive.

RGCs aggregate input originating from rods and cones and project through axons in the optic nerve to several brain areas. The output of some RGCs, especially those involved in NIF-effects of light, is not only determined by rod/cone input. The so-called intrinsically photosensitive RGCs (ipRGCs) express the photopigment melanopsin. Light falling on the ipRGCs can change their membrane potential and spike rate even in the absence of rod/cone input.

Melanopsin has two stable isoforms. By absorbing a photon, the *11-cis* isoform changes to the *all-trans* isoform, promotes depolarization, and increases the spike rate

of the ipRGC. The resulting *all-trans* isoform first has to absorb a photon, of another wavelength, to restore its phototransductive capacity. Mure et al. (3) suggested that the phototransductive melanopsin isoform of humans is maximally sensitive to blue light (481 nm), that the restoration process from *all-trans* back to *11-cis* is maximally effective at orange light (587 nm), and that an equilibrium of switching between the two isoforms occurs with green light of 514 nm.

Based on these findings, Chellappa et al. (2) argue that sufficient prior exposure to monochromatic blue light will induce all melanopsin to adopt its nonphototransductive *all-trans* isoform. If this is indeed a stable isoform, and as long as the pool of phototransductive melanopsin is not restored by orange or full-spectrum light, ipRGCs will become less responsive to subsequent light. Light stimulus-induced output of ipRGCs to downstream brain areas will then represent only rod/cone-induced depolarization, but not melanopsin-induced depolarization. Conversely, sufficient prior exposure to monochromatic orange light will induce all melanopsin to adopt its phototransductive *11-cis* isoform. If this is indeed a stable isoform, and as long as the pool of phototransductive melanopsin is not degraded by blue or full-spectrum light, ipRGCs will remain optimally responsive to subsequent light. Light stimulus-induced output of ipRGCs to downstream brain areas will then represent both rod/cone-induced depolarization and melanopsin-induced depolarization.

Although long-lasting effects of monochromatic light exposure on subsequent sensitivity to light stimuli has been reported before (4), the interpretation that these findings support intrinsic bistability of ipRGCs (4) is not without debate. Alternative explanations propose that the conditioning monochromatic preexposures may induce changes upstream (e.g., in how ipRGCs will subsequently transduce signals originating from rods and cones) or downstream (e.g., by differential potentiation of the ipRGC-projection synapses) (5). Moreover, there are several cell-autonomous and nonautonomous

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mechanisms of regenerating melanopsin to its phototransductive isoform, some of which occur in darkness (6).

A BOLD Effect

Chellappa et al. (2) interpret their findings as indicative of postorange-enhanced sensitivity to the effects of light on brain activation during working memory. A no less exciting alternative interpretation may be considered as well. Brain activation during the working-memory task was derived by comparing it with brain activation during a simple control task. Light intensity modulated the difference in activation between the two tasks, and this modulatory acute effect of light intensity was boosted by prior exposure to orange light. An increase in the difference in activation between the two tasks, however, does not necessarily mean an increase of activation during the working-memory task. An increase in the difference could as well result from a decrease in activation during the baseline simple control task, with normal activation during the working-memory task. Unfortunately, the fMRI blood-oxygenation level-dependent (BOLD) signal provides a relative measure of the difference. Additional quantitative measures of baseline perfusion may be used to resolve this interpretation issue (7).

Is there any reason to consider that baseline activation during a simple control task could increase as a result of prior blue light exposure, or decrease after prior exposure to orange light? In fact, some previous work suggests that such a scenario cannot be excluded. Long-lasting effects of blue light on ipRGCs are not limited to a distribution change in the pool of phototransductive and nonphototransductive melanopsin isoforms. Melanopsin resembles invertebrate rhabdomeric photopigments, where it has been shown that blue light can induce a prolonged depolarizing after-potential, which in fly rhodopsin can persist for up to hours (8). Several studies using different assays suggest that ipRGCs can indeed show sustained depolarization, persisting after discontinuation of light stimulation for up to at least 20 min (9–12). This depolarization increases the spike rate above the intrinsic spontaneous rate that can even be found in dissociated ipRGCs (13). As a consequence, synaptic input to downstream brain areas increases. One of these downstream areas is the olivary pretectal nucleus that drives pupillary light reflexes. Indeed, the blue-specific prolonged depolarizing after-potential and its associated increase in spike rate

are reflected in the pupillary constriction that can be sustained after discontinuation of blue light exposure, in humans for at least 5 min (3). It is not unlikely that, in parallel, input to other downstream areas is similarly affected, including the sleep-promoting ventrolateral preoptic area (1, 14).

In diurnal species like humans, excitatory fibers from the retina may contact inhibitory neurons in the ventrolateral preoptic area, and thus promote alertness (14). Indeed, in humans, alertness increases with presleep blue light exposure and effects can persist for long into sleep (15–17). According to this scenario, the baseline spike rate of retinal ganglion cells would remain highest after blue light, medium after green light, and lowest after orange light, and so would the excitatory output to the downstream areas that it encodes. In the protocol used by Chellappa et al. (2), prior blue relative to prior orange light may indeed have increased the baseline activation of structures involved in alertness. This suggestion is supported by the finding that none of the areas that responded differentially to light modulation depending on prior color exposure are normally activated during the working-memory task. Rather, areas showed up that are involved in alertness and additional, possibly compensatory, executive control. These areas may not have to be recruited above normal activation under baseline conditions, but may have to normalize their activation to this level after having been tonically suppressed or activated by an altered ipRGC spike rate.

A Bold Hypothesis

The above discussion suggests that it might even be possible to use monochromatic orange light to minimize baseline ipRGC spike rate, and consequently the baseline activation of downstream brain areas they project to, not only their response to light. A few studies suggest that this may indeed happen under certain conditions. For example, alertness-reducing effects of amber light can persist for long into sleep (15–17). Another observation is that a red filter can strongly alleviate migraine pain (17), which involves the majority of the brain areas that Chellappa et al. (2) found to be sensitive to prior color exposure, including the prefrontal cortex, pulvinar, and amygdala (18). In two studies, effects were present but not interpreted accordingly. In one study (19), monochromatic light of 555 nm, a wavelength longer than the 514-nm isobestic equilibrium point of switching between the two melanopsin isoforms (3), promoted electroencephalographic slow-wave activity, the principal marker of sleep pressure. Finally, using the same monochromatic light, Vandewalle's group reported deactivation of similar prefrontal cortex and thalamus areas as in their present report (2, 20). Concertedly, these findings support the exciting possibility that light of above isobestic wavelength may even be used to promote sleep. The consistent brain imaging findings presented during the last decade by the Vandewalle laboratory provide solid ground for further work to understand the mechanisms underlying the intriguing effects of color exposure on brain activation.

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