I & Vision
Research Centre

Myopia Control: City Lights, Blood, Antagonist Action
Part II

Image: Moth meme with cityscapes from Pexels

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In Part II of this myopia control review, a bit about spectral nutrition, the evolution of vision, and the effects of red, violet, and green wavelengths will be covered. Artificial techniques, neural effects, the conclusion, and select references for 'Myopia Control: City Lights, Blood, Antagonist Action' will be uploaded separately as a part III for clarity and readability.

Part II: Sights, Lights, and Brain States

Even as we look for myopia causes and corrections anterior to and at the cornea, damage to the retina, social lives, or within the brain are major concerns. Changes to cultural and sensory environments have developmental and even neurodegenerational consequences in later life, so a great deal of attention is being paid to detecting and altering modern disease-causing stimuli to lower the future burden of public health problems.

Safe to assume few will have much choice about education years and intensity anymore, but something about how we do that could make a difference to ocular health and reduction of myopia prevalence. Interestingly, Sweden, Norway, and Denmark are some of the least affected countries in terms of myopia rates and progression. While we can certainly point to genetic and anatomical factors, for some decades they have had a unique value-based approach to childhood education too. Yet again defying global trends, Sweden recently announced reductions in technology-mediated education, flagging the possibility that digital tools impair learning. They'll soon be reverting to traditional methods including penmanship and printed textbooks.

This is a major contrast to the world's most myopic populations – South Korea, Taiwan, Singapore, China, and Japan – which have some of the most culturally competitive and heavily digitalised education systems and societies. Another difference is that the majority of these populations reside in high density urban zones and are thus exposed to significant night time artificial illumination. Great for industrialisation, 24-hour mobility, and policing. Not so great for sleep.

Evolutionary mismatches with new technologies are not uncommon, as what was once adaptive becomes maladaptive, for example rising rates of obesity from manufactured food and drinks, or alcoholism from sudden availability of fermented beverages instead of nutritionally advantageous rotting fruits. Parrots seem to share our maladaptive predilections for alcohol and drugs, along with several other species like reindeer and even butterflies and moths, which are more partial to sugary wine, rum, or ale. And lamps, until the clever ones evolve past it.

The new technological 'addictions' for our species include urban lifestyles, mass education, artificial lights, and digital media. Aside from the much-maligned blue light, red, green, and violet wavelengths in their relative as well as absolute doses affect our sensory cells and neural processing pathways. This contributes to the effect of our media use and 'spectral diet' (Webler et al., 2019) on tissues, circuits, and wellbeing.

Besides peripheral and subconscious visual elements, studies with blind and colourblind subjects demonstrate that non-classical photoreception, or non-image forming (NIF) light information, is causing responses to environmental cues through intrinsically-photosensitive retinal ganglion cells (ipRGCs) and other mechanisms. Below are some ways our post-industrial urbanising and digitalising environment may impact assorted photon detecting cells and brain activity, which may in turn be leading to not-so-adaptive axial elongation along with other ocular, cellular, and neurological pathologies.

Overview of Vision and Urban & Digitalised Spectral Nutrition

Affordable tools for precisely measuring child daily spectral exposures may soon be available (e.g. Spectrace announced in 2019), and could be used to improve quality of studies that seek to investigate the effects of light characteristics on myopia development. For example, M. Li et al. (2023) found that reported time outdoors for Singaporean children was protective against myopia but not light level, timing, or frequency. Colour properties were not included, except indirectly by checking daylight exposure times which have different spectral compositions.

Light colour composition could be having some epigenetic effects. For example, arrhythmic blue or violet deficiency for pregnant mothers might be amongst several causes of earlier onset myopia in children (on reduced methylation in Singaporean neonates, see Seow et al. 2019; on lens-induced myopia in mice, see Xiaoyan et al. 2021). After all, assorted colours are able to determine the neurostransmitter profiles and mood of adult offspring of exposed pregnant rats. Some kind of colour vision factor seems to be at play because myopia is less of an issue for individuals around the world that are colour-deficient, with high incidence of this in Scandinavia (Gan et al. 2022). Reasons proposed involved Long and Medium wavelength (L for red, M for green) cone ratios or interactions that affect emmetropisation (Ibid.). Reduced S-cone (blue) sensitivity and lower central retinal distributions have also been proposed as one of the many mechanisms involved in myopia development, and in general, all photoreceptor cell types may take several years to fully mature after birth (Hussey et al., 2022).

Colourblind individuals lack the usual opsins, which are photo-detecting pigments on cone type photoreceptors specific to different colour wavelengths. Rods which we use for dimly lit vision and intrinsically photosensitive retinal ganglion cells (ipRGCs) that we use for circadian and other non-visual purposes, have rhodopsin and melanopsin respectively, with their own peak sensitivities in the green-blue and blue range. Not covered here is the role that ipRGCs and 480 nm light may play in myopia development (A. Liu et al., 2022) and the modulation of non-visual neural activity, for example in auditory and other attentional tasks, correlated with pupil size (Paparella et al., 2023).

The process for expression and opsin-type fate determination of different cone cells in the human retina remains mysterious, and the 'requisite mosaic' of red, green, and blue cones for adult trichromatic vision was thought to be a miraculous byproduct of spatial vision (Jacobs & Nathans, 2009) and ontogenetic cellular signalling. One theory is that levels of retinoic acid in early development (linked to genetic polymorphisms) influence M versus L cone subtype fates, and therefore eventual distribution and ratios across the retina (Hadyniak et al. 2021). L cones seem to appear last and are more common in the peripheral retina, if you decide to believe the organoids (Ibid.). The S cone is ancient, demonstrating lower variability in human populations and developing first, contingent upon thyroid hormones (Hussey et al., 2022). Red-green discrimination through separate but adjacent L and M cones is a later developmental process but a more recent genetic innovation that conferred significant advantages to Old World and a few New World primates.

Cell Type	Estimated Number	Response Type	Project to
Rods	120 million	Rapid ; Low Light, Motion Rod Peak: 498 nm	Bipolar, Amacrine cells, Horizontal cells Then RGCs and ipRGCs
Cones	5 million L – ˜60% M – ˜30% S – ˜8%	Very Rapid ; Light, Colour, & Fine Detail Vision L peak: 561 nm M peak: 531 nm S peak: 430 nm	Bipolar, Amacrine, Horizontal Cells Then RGCs and ipRGCs
Retinal Ganglion Cells (RGCs) Various subtypes	1.07 million	Assorted; Input received modulated by other retinal cells	Lateral Geniculate Nucleus (LGN) of Thalamus; Other midbrain nuclei
Intrinsically Photosensitive Retinal Ganglion Cells (ipRGCs) Several Subtypes	7,000	Slow Sustained; via Cones ipRGC peak: 482 nm → Pupil Response → Circadian Patterns → Attentional Networks	Suprachiasmatic Nucleus (SCN) of Hypothalamus + other thalamic, hypothalamic, and brainstem areas

Above Table: Human Photon Processing Cell Types, compiled from Mure (2021); Kim et al. (2021); Hussey et al. (2022), Jacobs & Nathans, 2009; Higham, 2018, Want, 2019; Estimates from multiple sources, noting that L/M cone numbers and ratios can vary greatly across individuals.

Light, colour, texture, L and M cone ratios, or retinal-to-cortical processing variations could be behind results seen in Beijing, where green zones reduced myopia progression for adjacent schoolchildren (Zhang et al., 2023), and how being outdoors but not necessarily being physically active may do the same for all child cohorts (Muralidharan et al., 2021). The way our eyes and brain respond to external information, whether it's the patterns of natural landscapes and biological systems versus glass, built walls and cityscapes, or coding how to prioritise near-work information versus other activities, involves switching between different circuits and pathways. Retinal signals transmitted through the lateral geniculate nucleus (LGN) of the thalamus – the latter being the central sensory info receiver and relayer for the primate brain – run alongside parietal-thalamic pathways that regulate attention and 'profoundly' modulate brain activity for optimal function in response to context (Paparella et al., 2023). In prenatal, childhood, and adult windows it is not surprising that there could be a mutually reinforcing effect between the neural activity and the retina, which is the dominant human sensory organ and part of our brain tissue called the diencephalon, which also includes the thalamus.

We're not the only species adversely affected by modern infrastructure. Birds crashing into power lines and nocturnal light-navigating creatures like moths, even plants, have their routines and survival imperiled by artificial structures and light pollution. The effect of Artificial Light at Night (ALAN) on nocturnal animal visual systems was analysed in an ecological approach by Stockl & Foster (2022). According to the paper, the industrial age upended the ratio of celestial to terrestrial light sources, the former comprising the sun, moon, and stars as photonic shapers of earthly visual systems. Night-dwellers operating in high-noise low-signal conditions adapted to increase contrast and photon sensitivity, optimising via shorter focal lengths, larger photoreceptors, larger lenses, and wider pupils. Cellular and neural wiring are demonstrated to be crucial components of the stimuli-to-behaviour process, with light-pollution distribution patterns impeding neural response (Stockl & Foster 2022, Figure 5). The authors of this paper as well as (Webler et al., 2019) suggest hyperspectral imaging systems as a next step. Their approach and focus on visual and neural mechanisms in relation to artificial light could be appropriate for human studies and subsequent urban health policy proposals.

Light Emitting-Diodes (LEDs) are some of the worst offenders in terms of bright, blue-white, widely scattering and deleterious glare. In an article by Patel, Perry, Wolfe, & Sabens (2023), LED light pollution was characterised as potentially carcinogenic and disruptive of immune function, both consequences of induced circadian rhythm dysfunction. Lower lumen and warmer (closer to orange) hues are suggested as better options. The choice of which LED type makes a difference not just to energy costs but night sky pollution, human health, and animal extinctions. It may even make a difference to human cone subtype specification, as ALAN has been linked to thyroid dysfunction as well as cellular stress, mitochondrial damage, and apoptosis in several species. This is possibly due to inhibition of night-linked melatonin production and this antioxidants ability to counteract oxidative stress and improve mitochondrial function (On neuroprotection, see Beaupre et al., 2021).

Using the accused poison as antidote, light therapy has an increasing number of biomedical applications across human age groups. For the elderly, wavelengths of 670 nm may maintain cone health through enhanced mitochondrial function, or could improve sleep quality by providing a little extra response capability to aged ipRGCs. Research into applications for myopia control and pain management is accelerating, with a green light project receiving a grant for post-surgical applications by the US Army in September. At opposite ends of the semi-visible spectrums, red and violet bands have been proposed for myopia control.

Photoperiod is much less popular as a research topic at the moment, but it is generally understood that refractive error and eyeball elongation tend to accelerate when daylight hours are reduced during winter. This makes it even more peculiar that Scandinavians experience so little myopia, but such an abundance of darkness over the year near the North Pole. The way our planet interacts with the persnickety sun influences the spectral composition of sights, seasons, locations, and time of day. Diurnal variation yields a sort of human eyeball biorhythm, and life patterns that affects all living things. Even plants have photoreceptors that affect their colours, morphologies, and growth cycles.

For humans, in some studies and experiments the choroid thins for red and green wavelengths while it thickens for blue, others show the opposite or not quite the same effects. The effects of blue light are more consistent, and it functions as an 'awaken' and attention signal for our brains (Paparella et al., 2023). Unlike nocturnal species such as mice, we are quite sensitive to non-visual blue light for regulation of our circadian clock and sleep cycle (Xiaoyan et al. 2021). However, like mice, photoperiod and its implicit blue spectral properties can still affect our internal dopamine and melatonin dynamics, allowing the processing of seasonal cues and accordingly altering hormone and neural activity (Jameson et al., 2023).

Before we decide on whether or not our species could be switching activity patterns – from diurnal to electrical – and suffering the short-sighted (yes, pun) consequences: A momentary detour through the realm of noctural, diurnal, crepuscular, and aquatic vision.

Ecologically Logical Vision: Sun, Food, Fractals

Did you know that some lizards have a light-sensing 'third eye' on their heads? Now you do. These non-visual parietal eyes allow them to navigate terrain using the sun as a compass, also acting as a thermoregulator and circadian rhythm-setter, similar to our ipRGCs. Although under the skull and technically blind, these nifty spots signal danger to the organism when light is blocked overhead, triggering an instinctive flee response to looming predators even in semi-domesticated pets. Mammals like us may have turned this third eye into the pineal gland, which we use to secrete melatonin that regulates the sleep-wake cycle according to doses of sunlight from the suprachiasmatic nuclues (SCN) (Beaupre et al., 2021).

Eyeless and eye-degraded cave spiders (*Leptonetela*) have also been found to retain photoresponse and phototransduction pathway genes that carry light information to the brain. Why? Well, according to K. Wang et al. (2023), they use blue-green light detection (by Rh2 opsins only) and its avoidance as a proxy stimuli for aridity avoidance, which determines survival and is thus under purifying selection. Why again? Because apparently if they did *not* have an overruling photophobic response, they seem to prefer and would run towards drought conditions at bright cave entrances and die. To be fair, high humidity conditions mean they risk death by water droplet. It's a hard life.

Turtles, birds, and crocodiles lost functional versions of the opsins for parietal sensory organs several million years back, replacing them genetically with more ecologically functional protein-coding genes. Crocodiles became nocturnal, prioritising rods for low light (scotopic) vision to hunt and losing photoprotective compounds in their skin. Being carnivorous (plants and their ripe fruits = irrelevant) they are also blissfully colourblind, losing 2 of the original 4 opsin colour 'channels' (Caspermeyer, 2017). Whales living in the deep blue sea did away with blue-detecting S-cones, and therefore only perceive stimuli detected by their red-sensitive L-cones.

Bird sight evolved in the opposite direction, which is frankly unsurprising given that they literally went in the opposite direction (up), and rather than losing the ancient blue S-type cones kept ultraviolet vision via a fourth cone type. Sight in ultraviolet allows them to detect meaningful UV information in plants and breeding partner feathers, and humans may do the same for subtle differences in reds that indicate health, hormones, and blood flow relevant to social communication.

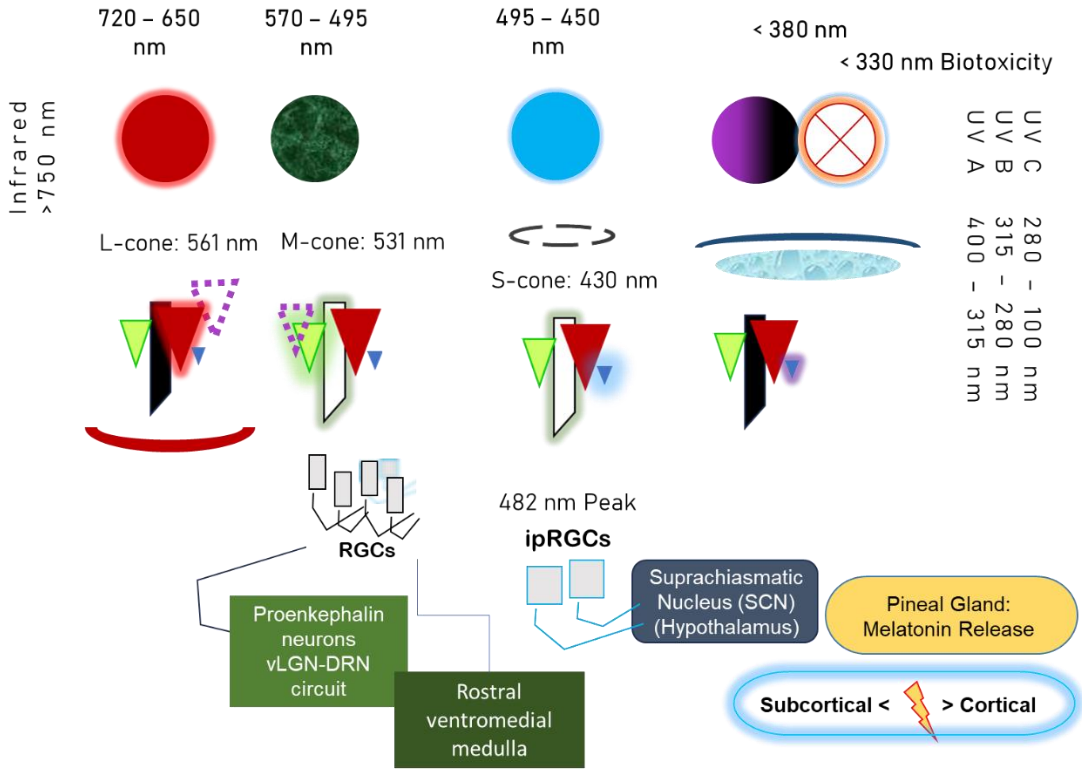
There is a general association between the number of cone types an animal has and how colourful they appear to us, with several butterfly species and the magnificent mantis shrimp possessing the most, but to detect rather than discriminate colours (Want, 2019). Jewel beetles evolved to use their glorious colours against birds, with iridescent shifts encouraging suspicion and avoidance instead of predation. In a simpler version, some reptiles mimic the bright colours of highly venomous kin for deterrence.

As for fractals, you can think of them as the opposite of highly salient objects (prominent, in terms of instinctual or learned attentional priority, more in Part III) in an organisms visual environment. They are also an increasingly fashionable concept in mathematics, geometry, and complex biological data analysis. Perusal of the wide array of research topics with 'fractal' as a keyword is quite fascinating. The basic definition is that of an irregular geometric shape with increasingly small fractional dimensions and thus scaling symmetry, commonly seen in organic phenomena (Britannica, 2023). Fractal patterns characterise snowflakes and coastlines, vascular, synaptic, and floral arbours, as well as some categories of classical architecture and geometric art. In the absence of learned salience, fractals in peripheral vision do not automatically capture attention or trigger focused gaze redirection (See Ghazizadeh et al., 2016, with random colourful polygons as fractal stimuli), which is probably why they are experienced as pleasant and relaxing regardless of cultural background (Taylor, 2017).

Organic and irregular fractal sights strike a fine balance between regularity and 'surprise' in our visual environment, with many applications for biophilic design. The lack of surprise elements and fractionated spaces in highly regular, top-down engineered environments can yield an artificial, suppressive, and helplessness effect that makes not just us (Robles et al., 2021), but several mammalian species quite uncomfortable. This might have something to do with predation risk, lack of personalised objects and agency, and thus higher cognitive burden from altered neural network activity, increasing stress. By contrast, fractals in the mid-complexity range (denoted "D" with rating from low of 1.1 to 1.9 for high) make our visual system, and thus overall brain state, more efficient, relaxed, and content (Taylor & Spehar, 2016).

All the above underscores that ocular morphology, along with the assortment and organisation of visual and non-visual eye cells in each species is a product of environmental constraints and opportunities. We are of course included, and one of the major evolutionary events for mammalian vision was the nocturnal bottleneck. After a great die-off of day-roaming cold-blooded carnivores, mammal populations swarmed into a new daylit niche. Some lost insect-digesting enzymes, and some developed trichromatic (3-colour vision) and appropriate wiring for functional neural processes to take advantage of photopic (daylight) conditions for fruit and mate selection (Jacobs & Nathans, 2009; Higham, 2018). Even for butterflies, Sondhi et al. (2021) found that light availability can drive the development of more colour-detecting opsin variants.

As a diurnal species, our choroids are trained to adjust thickness according to a daily rhythm (Ostrin et al., 2023) and we additionally evolved sun-screening absorbic acid in the lens (Schwab, 2017), which protects our sight from UV-damage until replaced in cataract surgery. After surgery, this then allows for an expansion of patient vision into the ultraviolet range, without having to invent a new cone! High flying birds also adjusted this lens technique, with UV absorbance shifting as the species shifts altitude and reflective snow-coverage (Zawadzka et al., 2021). Last, as a critique of the the past century in state-led top-down urban planning and design, our eye-brains seem not to have evolved past the need for organic sights, unregulated greenery, and regular display of fractal patterns (Brielmann et al., 2022).



By IVRC: Selected light wavelengths, human photoreceptors, and other structures. Rods are maximally activated by ~500 nm wavelengths. Red light affects choroidal thickness, green reduces pain perception through multiple pathways, blue regulates melatonin release, yields the pupil response, cortical network shifts, and is the main activator for ipRGCs, while violet-ultraviolet is mostly filtered by the lens.

Occasionally, humans (female) will have a fourth photoreceptor type in the medium or long-wavelength range that expands the set of perceived and distinct colours (Jordan & Mollon, 2019).

On With the Lights

Infrared and Red Light Therapy

We may not have a parietal eye, but it is theorised that chromophores in our brain tissue are able to absord certain wavelengths that make it past the hair and skull. This then affects cellular and neural activity within (See Dos Santos Cardoso et al., 2021), which is why techniques like non-ocular photobiomodulation (PBM) seem to work. This light response isn't directly and quickly linked to a motor action or behaviour at the organism level, but certain near-infrared bandwidths (800 – 1100 nm) may be used to influence depression and brain health over time, to control inflammation, or after injury. Nitric oxide modulation is another target of ongoing PBM and biophotonics research, with Kashiwagi et al. (2023) and Yokomizo et al. (2023) proposing the near infrared II bandwidth (1000 – 1700 nm) that has fewer mutagenic effects for cardiovascular and neural applications.

Red light is very helpfully colour-coded for blood-related applications in ocular disease. Last month in pathology, 'photodynamic combination therapy' developed by a team at the University of Hong Kong utilised a red light-activated nanomedicine for macular degeneration (AMD) that blasts apart neovascular formations in wet forms of the disease. According to the study, this photoactivatable nanosystem (Di-DAS-VER NPs, using 690nm, at 100 mW cm^(−2)) would be an efficient and safer alternative to monthly anti-vascular endothelial growth factor injections (Xu et al. 2023). No mention is made of the potential for unintentional activation by environmental and medical red light sources, which is advisable considering the projected increase of photo-therapeutic devices that use red bandwidths.

Again for AMD-related retinal degeneration, photobiomodulation might be used on its own or in tandem with nutritional supplementation. Here the mechanism would match that of non-ocular PBM where cytochrome C oxidase activity is enhanced to eventually reduce neuroinflammation and glial cell reactions, preserving vision. As an added consideration, supplements like AREDS2 are often recommended for AMD, with formulae undergoing regular updates on the basis of research. However, it's not always easy to predict how medication, nutrition, and procedures could interact – and that's leaving out potential genetic and temporal interactions at the cellular level. Using albino rats exposed to retinal light damage, Di Paolo (2021) varied a PBM (670 nm) and dietary saffron sequential protocol to demonstrate how the two have antagonistic effects when given simultaneously, but saffron after PBM and light damage slowed initial inflammation. PBM treatment preceding light damage conditions showed the least destruction. The effect of each protocol on the outer nuclei layer (ONL) and retinal thickness is shown in the study's Figure 1.

For childhood myopia, 650 nm repeated low frequency red light therapy (RLRL) has demonstrated reductions of axial elongation in Chinese cohorts, though it is unclear whether choroidal thickening could be due to inflammation or damage response. The positive interpretation is that this might have something to do with increasing choroidal blood flow and circulation to improve ocular function and health. Successful orthokeratology and 500 lux morning light-delivery glasses (See Muralidharan et al. 2021) have a similar effect on choroid thickness over time, while Gingko Biloba extract can suppress myopia progression in mice through improvement of choroidal circulation. Choroidal blood flow has even been proposed as a type of 'rapid predictive index' for myopia onset and new therapeutic evaluation, the mechanism suspected being inducement of scleral hypoxia and receptor-linked signalling pathways that promote eyeball elongation (Zhou et al., 2021; Liu et al., 2021).

Another preventive/protective avenue involves media choices. In human subjects, inducing positive defocus by sitting close to a movie screen was found to increase choroidal blood flow and inversely affect axial length (Swiatczak, 2022). Swiatczak and Schaeffel (2022) also found that movies digitally altered to be red-focused and blue-filtered led to shortened eyeballs in pre-myopic viewers, suggesting that more photodynamically red movies could be a non-invasive strategy for myopia control. Discrepant effects would probably extend into visual and even non-visual segments of the brain. As an example, Argiles et al. (2022) showed decreased functional connectivity in attentional networks following red (635 nm) light exposure. These are regions associated with more external goal-oriented tasks. Visual networks, memory, and internal-focused functions were comparatively more active in response to red than the blue (464 nm) or green (516 nm) light.

In the case of eyes damaged by axial elongation, Japan has just started a trial for low-level red light therapy in *adult* high myopia. The study hypothesises that a narrow red band will be able to thicken posterior membranes and reduce ongoing damage. If viable, the therapeutic may be valid for the expanding cohort of university attendees and professions that are increasingly affected by adult myopia (Review by Bullimore et al., 2023). However, this still means that the body of research for low-level red-light methods in ocular disease management covers only East Asian eyes, and other than rebound and child safety and comfort concerns, results may not be globally generalisable.

Violet – Ultraviolet: Anti-Myopic, Bird Sight, Cosmic Explosions, Biotoxicity

Xiaoyan et al. in 2021 proposed that the lack of violet (360 – 400 nm) and abundance of artificial blue-enriched light in modern environments were causes of circadian disruption as well as the myopia boom, highlighting the role of UV-sensitive OPN5. The myopia therapeutic suggested based on the mouse model was 3 hours of post-dusk violet light. Perhaps reductions of violet and ultraviolet light through glass mediums and reflected off built materials (Webler et al., 2019) is why just sitting by the window doesn't seem to work as well as time outdoors for young myopes.

In another mouse study, Jeong et al. (2023), varied violet light transmittance through lenses and found that the 70% and 100% exposure intensities (26 and 40 µW/cm2) suppressed myopic progression and choroidal thinning. Like red light, the authors mention that violet bands may modulate choroidal blood flow, with neuropsin activity somehow leading to an increase and thickening effect.

There are alternative explanations from a diurnal tree shrew and other animal models, though. It may not be the lack of a specific colour band *per se*, but restricted exposures to full spectral bandwidths in artificially lit territories that is causing widespread axial elongation. A deficiency of defocus cues may be leading to STOP signal failure, and therefore slow but steady development of myopia (Khanal et al., 2023). Either way, smoothing out the blue and ramping up a greater range of violet and red could be valid options.

Several birds are evolutionarily primed for species-specific ultraviolet sight and contemporary benefits, including environmental protection. Example: One solution proposed for species protection from powerline collisions is the use of UV paint on wires, the sight of which alters flight patterns and permits a greater detection distance for avoidance, especially at night (Baasch et al., 2022). As this coating is beyond the range of human vision, the method doesn't affect human inhabitants.

As for our artificial ultraviolet sight, we are currently using UV telescopes and false-colour computerised conversions to observe solar activity, Jupiter, and other distant phenomena of the universe. You know, the usual. Hot young stars, enormous space explosions, and habitable planet candidates. The Hubble telescope, our only deep space viewing option with ultraviolet abilities, could soon be repaired or replaced by the Canadian CASTOR (Cosmological Advanced Survey Telescope for Optical and UV Research) so that we don't miss out on anything exciting (Howell, 2023).

Naturally we fly blind in the UV bandwidth but there's a good reason for that, with gratitude to the planet's atmosphere and our crystallin lens (Schwab, 2017) for protecting ocular cells from high energy, short wavelength damage. Even birds would not be able handle exposure to biotoxic bands of UV (<330 nm) (Zawadzka et al., 2021) that blasts apart DNA and RNA, which is one of the reasons for its use as a potent germicide. Germicidal UV serves as an excellent case study in why our rush to technologically over-correct our environment after one proven benefit, instead of carefully evaluating complex biochemical interactions and consequences, can be a bad idea.

The past few years have yielded a bit of a sterilisation boom, and one strategy in medical spaces is to strongly ventilate or blast the place with ultraviolet light to unravel the DNA of lurking microbes, many of which are becoming resistant to our antibiotics and even chemical germicides. A pretty substantial side-effect of indoor germicidal UV was found in October by researchers at MIT. Although UV (222 nm) to reduce indoor pathogen load is categorised as safe for humans, when improperly ventilated this radiation bandwidth chemically interacts with indoor air to yield a pollutant mixture of ozone and other harmful compounds.

Given these properties, we could afford to be a little extra cautious at this end of the light therapeutic spectrum, as it has already been bad enough with mass applications in artificial blue (See L. Wang et al. 2023 on blue phototoxicity effects in retina, mitochondria). Perhaps some artificial intelligence discoveries of new antiobitic subclasses will buy us some time, but if not, it's time to ventilate and green-scape hospital spaces (Jamshidi et al., 2020).

Green – Pain Killer, Thalamic Filter

Plants are pretty good at alleviating stress in offices and promoting recovery and pain reduction in hospital patients (Nieberler-Walker et al., 2023; Taylor, 2017). Part of that could be that they act as low-maintenance and pleasantly fractionated pets, and partly because they are green.

Green light is a little strange in terms of characteristics and effects, and perhaps this is due to it being smack in the middle of the visible spectrum for humans, although our cone peak sensitivities are unevenly spaced to maximise fine red-green colour discrimination (Higham, 2018). Nevertheless, the human retina is most sensitive to green light, meaning it has a higher visible impact and causes us to perceive plants surrounding us as definitely green, even though this bandwidth is only slightly enriched in leaves.

Natural greenery seems to limit myopia progression for urban children, but deliberate green light (510 nm) treatment can actually *induce* myopia and neurodegenerative disease in mouse models. Ji et al. (2022; 2023) conducted transcriptomic and proteomic analyses of green-light-induced myopia (lens-induced, LIM) in mice and found that differential genes and protein expression indicated dysregulation of energy, vitamin, and carbohydrate metabolism. Dopamine levels and mitochondrial function were decreased in LIM eyes after 4 weeks, and Igf2bp1 (insulin like growth factor 2 mRNA binding protein 1) is proposed as a candidate biomarker.

Despite inconclusive results on myopia, what green light is particularly good at, even for red-green colourblind patients, is pain reduction. Work on migraine photophobia in 2016 revealed that blue light triggered migraine pain in blind subjects, while green light exposures were the only colour to reduce pain (Kritz, 2016). Noseda et al. (2016) showed that migraine photophobia was largely a result of cone-driven retinal pathways and thalamic activity. Green (530 nm) had a relatively weak ability to induce firing in thalamic neurons, and thus decreased pain ratings by up to 15% in some subjects. At the level of the cortex in retino-thalamo-cortical pathway, P2 amplitudes (a measure of brain activity) in response to green were smaller than for blue, amber, and red. As a precautionary note, 91% of the patients in this study were female. Given distinct colour perception and processing abilities in men and women from retinal to cortical levels, repeating the study with a male cohort could be interesting.

Since then, green eyeglasses have been used in treatment of fibromyalgia, with positive results in terms of opiod use and anxiety reductions, and the fact that the patients did not want to give the glasses back after the experiment. According to P. Gulur of Duke University School of Medicine interviewed in Kirkendoll (2022), the most effective spectral bands were at either end of the green wavelength, around 495 and 570 nm. Similar work is underway at the University of Arizona, with white then green LED light strips used by fibromyalgia patients – 95% female – for ten weeks each (Pigott, 2023A; Martin et al., 2021). Their pain, daily function, and quality of life improved following the green light use. The same team recently received a research grant for green light therapy applications in post-surgical recovery (Pigott, 2023B). The theory is that green light is transmitted to the rostral ventromedial medulla, altering its activity as well as the chemical levels and immune cell activity of patients. In that sense, it could be able to reduce pain and inflammation.

Studies of arthritic mice highlighted a different route. Through cones, *and* rods, and proenkephalin neurons in the ventrolateral geniculate nucleus (vLGN) of the thalamus, the green signal eventually makes its way to the dorsal raphe nucleus in the brainstem which then modulates pain sensitivity (Tang et al., 2022). Several scientists commenting on the study in Manjarrez (2022) mention that there are likely multiple cells and pathways involved in green light's analgesic effect, and this is realistic, as our eyes have a vast array of visual and non-visual functions, many we still don't know about or understand.

Therefore, it may not be efficient to propose biomedical solutions targeted to a single aspect of optimisation for ocular, mental, and bodily health. This is where a lifestyle reversal or virtual immersions could come in.

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Continued in Part III. Until then: