**Myopia Control: City Lights, Blood, Antagonist Action**
**Part III**

*Could virtually delivering natural, fractal, and social stimuli keep modern eye-brains healthy and happy? Photo by Fei Wang (Pexels), edited.*

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*In Part III of this myopia control update: Artificial solutions for myopia and other health problems, the possible role of the salience network, and the link between myopia, neural activity, and neurodegeneration. The question is posed as to how to talk to patients about these risks and then, at last, the three-part article conclusion.*

*You might find it convenient to refer to a brain map deeper down the article, e.g. some from* ***https://brain.oit.duke.edu/lab02/lab02.html***

**Artificial Photic Signals as 'Outdoor Time'**

Going beyond singular factors and mechanistic interventions, how about artificially delivering natural surroundings as a myopia preventive? In consideration of myopic and ageing populations, nature plus various forms of photo-therapy show promise as minimally invasive biomedical interventions, possibly even preventives. With ongoing technological advances, these could be provided virtually for millions of patients, urbanites, and school children with limited opportunities or time to spare for visual baths in the great outdoors.

Some scientists have proposed digital therapeutics and others, virtual reality (VR) for the management of neurodegenerative conditions, developmental disorders, and myopia. The advantages of VR and other advances in computing theoretically lie in precise analytics and simulation. However, we aren't there yet and have to deal with a host of other ocular complications from digital device use first (Jonnakuti and Frankfort, 2023). This doesn't just pertain to impacts on child minds and vision, although there are important developmental windows at younger ages, hence the age restriction for commercial VR devices (ages 13 and up). Augmented (AR), mixed (MR), and virtual reality tools are being used for adult occupations ranging from surgical training to foreign combat and domestic security roles. It is imperative to understand how these may be affecting ocular tissue as well as how our minds process, react, adapt, and deal with this type of information.

In theory, by visually immersing the candidate through use of a head-mounted device (HMD) and altering multiple dimensions of sensory input, VR is able to initiate cortical reorganisation, which could mean rehabilitative rewiring of neural circuits. In that sense, if an artificial programme is able to capture and replicate a 'time outdoors' or otherwise 'enriched' visual environment, this could function as a protective measure for young children without requiring understanding of each causative factor for myopia or neural dysfunction. Computers after all can be designed for purpose, and are able to detect colour and light properties that a human cannot, which is why deep learning is becoming such a popular topic for medical diagnostics (example on anaemia diagnosis from external eye images). Both VR and augmented reality (AR) methods are also capable of maintaining peripheral defocus in bland indoor environments as a myopia control technique to supplement optimal spectral delivery. However, this depends on really good specs in terms of field of view and high resolution capabilities of the device, with design attention to image forming on the central *and* peripheral retina, and hopefully without tradeoffs like ocular light-burn from super bright displays.

Beyond delivery of artificial environments and stimuli, extra operations, sensors, and parts can be added to a hypothetical VR or AR device for biomedical purposes, ranging from intraocular measurements (Efron, 2023) to feedback systems for improving hand-eye coordination. VR-based examinations and tests have already performed better than other assessment methods in detecting subtle cognitive deficits in Parkinson's and Alzheimer's patients, and offer other advantages such as higher ecological validity (Sokolowska, 2023). In addition, VR has been applied to improving gaze perception for the visually impaired, thus enhancing the sense of social presence which enhances quality of life and sense of engagement in the world around them.

As part of a systematic review on VR in human health, Ali et al. (2023) listed several applications in the category of ocular disorders, including VR for myopia. The authors note that this technique is not receiving the same amount of attention as artificial intelligence (AI) in healthcare, even though there seems to be potential for enhancing cognitive function, improving vision, and treating motor disorders. In myopia, artificial intelligence is already in use for risk assessment, orthokeratology fitting, and disease classification, and has potential to replace or support human graders in some tasks. More applications in the vision sciences are expected as the variety of methods expands, with multimodal and explainable AI as some examples given in Y. Li et al. (2023), a review of AI and digital solutions for myopia. Chan et al. (2023) prepared a review specific to VR interventions in amblyopia, strabismus, and myopia. So far, amblyopia and rehabilitation techniques have seen some of the better results from VR interventions.

In Ali et al. (2023), it is explained that a binocular visual function (BVF) balance training delivered by VR engages the ciliary muscles to improve ocular function and blood supply. However, one of the major articles cited with positive results for control of juvenile myopia from a combination treatment of atropine and VR-based BVF was retracted in August 2023. VR applications for macular degeneration, a significant age-related complication of myopia, are covered as training and mobility tools to enhance patient daily function and quality of life despite vision impairment (Ali et al., 2023).

Six of the 48 studies in the review by Chan et al. (2023) were on myopia, with techniques utilising commercial VR headsets. Prominently featured are methods employing games like Galaxy Wars, Temple Run, Mr. Cat's Adventures, and Lands End to find out how VR affects the binocular vision system, accommodation, and visual acuity. Game elements are more likely to engage adults as well as children, who may otherwise not comply with clinical advice for myopia management. Interestingly, as adult myopes are adapted to operating in near work lifestyles, Panfili et al. (2021) found that severe myopes (-3 Dioptres or worse) can see better in VR headsets. Another unexpected finding was choroidal thickness increases in adults following VR use, possibly due to 'lead of accommodation' within HMDs. This is unlike other forms of near work which are myopiagenic and associated with focus delays. Other explanations for this observation in Turnbull and Phillips (2017) were temperature and headset-related changes in blood flow.

One of the barriers to VR acceptability is the need for a head-worn device, unlike augmented reality which may eventually make it to commercial contact lens format. Furthermore, Turnbull & Phillips (2017) noted how typical headsets are not matched to child pupillary distances, and there are some weight considerations. Risk of neck strain for younger children is a serious issues with the average HMD at over 0.6kg, imbalanced towards the anterior. Last, the effects on the developing motor system of children and plasticity changes in adults when virtual moves are discordant with bodily realities warrants a great deal of attention.

As in computer vision syndrome with symptoms ranging from eye strain, dry eyes, and headaches to upper body pain and muscle fatigue, multifaceted aspects of VR use may become a diagnosis if the products become a major part of daily work and social life. Demand side and real-world viability are still unclear, with AR and VR HMDs still causing adverse ocular and other side effects, like nausea, headaches, eye strain, and tunnel vision (Bastian, 2023; Roque, 2023; Jonnakuti and Frankfort, 2023). These are likely going to be persistent challenges without major changes to physical characteristics, price, resolution, and field of view for the devices.

However, the positive results of biomedical VR applications indicate that they can be used for good, as long as this is set as a priority in design and use (on brain health, see Sokolowska, 2023). For example, instead of headsets that are accused of acting as a beacon for enemy fire and cause of digital eye strain, could specific light bandwidths be incorporated into devices for vascular and cellular benefits?  If VR can be combined with photobiomodulation (PBM) in near-infrared bands (II and I), there is some potential as a neuroprotective measure or preventive therapy against age-related neurodegeneration (Ramakrishnan et al. 2024). Perhaps adjusting the light spectrum and peripheral stimuli based on findings in vision science could alleviate some of the physical and ocular problems from HMD use while limiting incidence of myopia for younger users, though this seems very distant.

In hospitals, aside from physical greening for the benefit of staff and patients or green light for reductions of pain and inflammation (covered in Part II), VR has been used in paediatric settings to reduce anxiety for orthopaedic patients and their parents. A combination of these approaches for remedy of civilisational diseases seems increasingly likely in future as access to natural sights and environments reduces, although bio-inspiration instead of biomimicry is recommended when the frame or medium is artificial (Taylor, 2021).

For the disabled, VR has already been applied to provide them with an opportunity to 'forest bathe' from indoor settings. Participants described outcomes of the virtual experience as 'beneficial emotional responses, developing coping strategies, adopting new perspectives, physiological relaxation, and feeling connected to community'. Even better, it motivated them to seek out their own physical experience in green spaces, an increase of agency and self-directed mobility (McEwan et al., 2023).

High levels of sympathetic arousal and stress common to populations in urban territories may be ameliorated by virtual provision of flora. Evidence-based medicine in Japan has shown positive physiological, emotional, and mental effects from purely visual stimuli of leafed plants such as roses, pansies, and Japanese cypress bonsai (Ochiai et al., 2017). Perhaps most relevant to stressed urban families with schoolchildren, plants in the home can affect reading comprehension as well as visual and mental fatigue recovery, especially when there's traffic or other ambient noise up to 50 decibels (Zhang et al., 2022). In the short-term, plants adversely affected 'work performance' because they decreased sympathetic arousal. This is probably protective for student/worker health and cognitive function over longer timelines, though. A 2022 meta-review (Han et al.) found improvements in cognition and 'significantly greater academic achievement' through the presence of indoor plants, with additional recommendations as to ventilation which is rather less easily simulated.

Tacked on to health-centric VR programmes and testing the benefits of virtually provisioned indoor greenery, it might also be possible to use 'socially facilitative' robots (Fraune et al., 2022; Kamino et al., 2023) or other types of artificial social agents to remedy some of the serious neural and psychological side effects of vision loss. This could then be protective of cognitive functions, self-confidence, and personal mobility in later life despite secondary blindness related to myopia.

So which sounds more appealing? Near-infrared ocular spa goggles, virtual forest-bathing at the dentist, Ikigai-boosting social robots, AR combat canine goggles, or entangling the activities of your visual cortex with a robodog?

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While you decide and before moving on to the effects of visual impairment on the brain, here is a table to quickly recap the factors and elements that seem to be involved in myopia:

| Novel Environment | Anterior to Ocular Surface | Anterior Eye | Mid and Posterior Cellular & Molecular Stew | | | Brain ? |
|---|---|---|---|---|---|---|
| Stimuli, Spaces, Surfaces & Activity Patterns | Dominant Near Visual Environment | Refractive Power | Posterior Vitreous Humor | Axial Length | Peripheral Retina | Suprachiasmatic Nucleus (SCN) |
| Light Spectrum | Filters | Cornea | Retina | Refractive Error | Visual and non-visual RGCs | Optic Nerve Sensory Input |
| Fractals | Optical Devices | Pupil | Choroid | Biochemical Forces | L/M cone ratio | Thalamic Relay & Computation |
| Object Salience | Spectacles | Lens | Sclera | Mechanical Forces | S-cone sensitivity | Visual Cortex |
| Ecological Relevance / Pressure | Contact Lenses | Ciliary Muscles | | | Rods & ON-bipolar cell dysfunction | Networks Activated |
| | | | | | | Functional connectivity, cortical and cognitive changes |
| | | | Dopamine Level & Receptors<br>Serotonin Receptors<br>Glycine and more? | | | |

*Figure by IVRC. Assorted external –> Eye <– brain locations and factors in myopia development. Specific genetic, transcriptomic (e.g. EGR1, FOS) and cultural factors not mentioned.*

Stone et al. (2024) point out that the growing number of molecular, transcriptomic, and genetic mechanisms identified in the myopia literature has prompted a shift to other – largely environmentally and behaviourally-based – therapeutic means and lifestyle changes for management. According to the study, neglected frontier topics at the moment include circadian biology, choroidal versus retinal gene expression, and distinct timelines and windows in pathogenic mechanisms (e.g. 4h; 24h). Linked to the latter is how time of day may be affecting genetic, cellular, and tissue behaviour in any of the interventions, which shouldn't be too difficult of a correction or data addition to make. Another possibility: Perhaps interventions in the optical, behavioural, and light dimensions have only been modestly successful so far because we are missing some crucial ecological elements.

**Other Urban Risk Factors: Lack of Fractals, Salience Network Changes?**

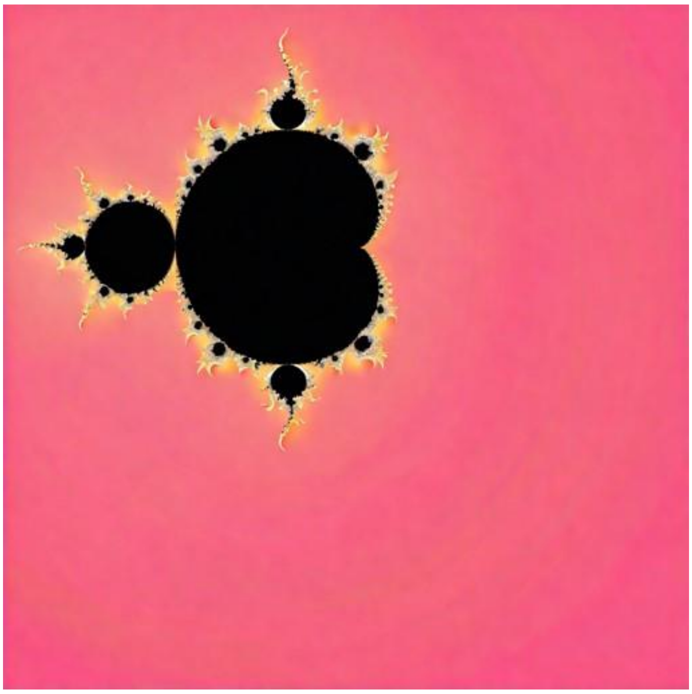
Since we are dedicating so much time to investigation of our inner microbiological workings, it would be only fair to explore the fluctuating visual properties of modern megacities and civilisations too. Altering environmental stimuli in clever ways could end up being more economically efficient and effective than pharmaceuticals and superficially, the aesthetics of urban life seem a viable target. For one thing, peripheral defocus is seen as a major culprit in eyeball elongation, and changes in the distribution, form, and attention towards peripheral visual stimuli could be affecting myopia development in small ways as well. Maybe this is indirectly evidenced by the 'time outdoors' factor and green zone provision as protective against onset and progression.

Studies shows that high population density and small home sizes are risk factors for greater axial length and refractive error (Grzybowski et al., 2020), while satellite imaging has been used to show that quantity of vegetation in urbanised countries is linked to lower myopia prevalence in 15 to 19-year olds. Trees and other types of non-flowering vegetation are usually various shades of green and complex but fractal, with edges that move harmlessly in the breeze.

These factors seem to be amongst many that matter, but we aren't sure why. One possibility is that the non-urban outside looks a little different, and the sights which are predominantly fractal and in terms of neural processing 'fluent' (Taylor & Spehar, 2016; Taylor, 2021) affect eye-brains differently. Fractal stimuli = easy on the mind, yielding restorative psychological, molecular, and neural states as opposed to cramming for an exam or staring at walls and building-lined streets, which have been described as 'soft' and 'hard' attention respectively (cited in Taylor, 2021). In a way, they exist as soothing photic background data with the pleasingly random quality that characterises multimodal organic stimuli. Although evolved as a general biological preference, aesthetic preferences for different levels of fractal complexity may be genetically based, involving polymorphisms for two genes that are within the retinal molecular milieu of axial elongation: Monoamine oxidase A (MAOA) and type 2 dopamine receptors (DRD2).

This relationship between fractals and neurological state also works in reverse. It seems that onset of neurological disease can be indicated by an artist's inability to produce works in their own unique fractal idiom. Beyond stress reduction, biophilic and natural structures may be beneficial in the realm of neurological disease for yielding a sense of wider territorial space instead of enclosure. This perception may affect the moods and mindset of even 'healthy' urban populations. Our basal ganglia which governs movement differentially computes built (manmade doorways) versus natural boundaries and features (hedges), as evidenced by a study on freezing-of-gait in Parkinson's patients. Fractals also specifically influence and characterise gaze and pupil dynamics (Taylor, 2021), with implications for ocular motion and the nerves and muscles involved in scoping out our post-industrial environment. Removal of this ecological factor from visual scenery could be affecting tissues and cell signalling pathways in ways that contribute to eye elongation given near work conditions. It is entirely unknown whether elements such as shape/movement predictability or edge characteristics in 'outdoor time' might matter more than vegetation *per se*. Or, it could involve something as simple as switching the brain's perception of space (e.g. am I inside?) and therefore attentional and ocular posture.

In the man-made sense, you may be familiar with fractals as a characteristic of artwork by Jackson Pollock, or in ritualistically produced Rorschach inkblots. Richard P. Taylor (University of Oregon, Physics Department) has studied fractals for some years, going from analysis of art and inkblots to proposals for biophilic urban design and even retinal implants. In a 2017 study of pareidolia induced by Rorschach images, his team found that: a) lower complexity of fractal shapes facilitated recognition of ecologically relevant patterns e.g. faces, animals b) this was further enhanced by left-right symmetry, and c) was strongly tied to jagged *edges* of the blots as opposed to the blot shapes as a whole. This effect on the visual system and processing areas of the brain is extended to applications for aesthetics and rebuilding of cities in more fractal, natural patterns as opposed to 'Euclidean' styles for public health benefit. In the conclusion of one of the more recent papers (Robles et al. 2023), both physical installations and virtual reality extensions are suggested to modify built environments for "WEIRD" and other populations.



Considering public tools for bio-inspired design in artificial spaces. Mandelbrot Fractal merged with a Golden Dragon (Zazow & Hotpot AI). Animation for drifting like a jellyfish would be the next step.

Fractals at pleasant levels of complexity seem to affect the brain in many ways. As implied by the data from cities, the lack of these and abundance of blue-enhanced LEDs versus other bulb types could be involved in myopia development too, which may be a call for a revolution in metropolitan décor and media. Progressively split edges and night mode for everyone! Both types of stimuli can affect one of the hardest working arcs in the brain: The salience network.

The salience network, often abbreviated to SN or SAN, refers to activity of the brain regions – the anterior insula and dorsal anterior cingulate cortex – that detect and direct attention and appropriate neurobiological resources to ecologically relevant stimuli. Under the Triple Network Model, The SN is believed to manage the switch between operations in the default mode network (DMN), or cognitive leisure and internal focus, to the central executive network (CEN, also known as the frontoparietal network) which is more effortful, task-focused, and goal-directive.

Fractals do not automatically draw gaze and attention unless a specific pattern recognised has acquired ecological relevance. This is done through learning, with attributions of reward, danger, or association with a conspecific. Quickly detecting salient objects (in natural environments typically amidst fractals in peripheral vision), then organising resources and behaviour to change this to focused gaze and attention, is one of the ways organisms adapt to and survive in complex environments (Ghazizadeh et al., 2016), also involving the dorsal attention network in the parietal lobe. Bright lights, the bright colours of fruits and flowers, faces, and novel, loud, or rapidly moving objects tend to have automatic salience, whereas others, like symbols and associations, have to be learned. Malfunctions in conditions like post-traumatic stress disorder (PTSD), where the SN is characterised as hyperactive, lead to heightened threat sensitivity, hypervigilance, and stress that negatively impacts daily functioning. By contrast, SN hypoactivity associated with autism during social situations can impede group functioning and relationship-building (Schimmelpfennig et al., 2023).

There is a lot of variability in salience network function as this seems to be one of the most active and by nature, the most contextually responsive circuit we have. In earlier investigation, Chen et al. (2016) on the basis of fMRI data proposed that temporal flexibility of this network predicts better executive functioning and cognitive flexibility of the individual. Currently, SN function is one of many factors being analysed for cognitive and affective disorders. However, it is hard to untangle mechanisms and results. Disruption to SN function can (but might not) lead to incorrect neural, mental, and behavioural responses to context through abnormal weighting of internal and external information. Dysfunction has therefore been associated with neuropsychiatric illnesses like schizophrenia (See Bolton et al. 2020). According to the review by Schimmelpfennig et al. (2023), SN hypoactivity has also been linked to neurodegenerative illness while hyperactive states are associated with conditions like depression, though likely the subtype, duration, and severity matters.

There are implications for spectral approaches to disease management. In healthy cohorts, Rs-fMRI (Argilés et al., 2022) studies show that functional connectivity *decreases* in all but the salience network upon blue light exposure. The presence of threat (which may include urgent memorisation for life-determing tests) as well as the subsequent release of norepinephrin lead to connectivity increases across the whole brain, but most of all, in the SN and amygdala. One of the receptors involved in the latter (alpha-adrenergic) response can be affected by high levels of atropine, and agonists have been seen to inhibit form-deprivation myopia in chicks.

Red light exposure, by contrast, increased DMN functional connectivity while green light increased FC in dorsal attention networks (superior parietal gyrus) which are responsible for top-down sensory direction and attention (Argilés et al., 2022). It's certainly an interesting possibility that our cognitive domains are colour-mediated, but further experiments are needed to test how meaningful the results are in real life and for different target populations.

fMRI studies on high myopia so far have shown some changes in terms of the salience network, with connectivity increasing in the left insula but decreasing in the left middle occipital gyrus compared to healthy controls (Ji et al., 2022). In Ji et al. (2023), hyperactivity was found between both sides of the visual cortex and the left anterior cingulate gyrus of the SN, which they characterised as a neural compensation for loss of other processing functions. Other than that, top-down control of visual attention was described as impaired, with enhancement of connectivity between the visual cortex and the superior parietal gyrus as the brain's attempt to repair the situation.

**Environmental Stimuli, Ageing, and Sensory-Neural Effects**

Both light and media have lasting effects on brain health and patterns. If used well, there is potential for improving elderly cognitive and cellular function. If not, recent neuroimaging studies have shown that media consumption through devices alters visual processing, brain function, and performance in children in a predominantly negative sense. The long-term consequences of tablet use by toddlers remain unknown. Also unknown are the factors which make it the worst device to use. Is it the tablet device itself, the lack of buttons, the size, the way they are held, or the distinctly unfractal cheaply animated cartoons watched on them? Someone should test that. Theories are mostly focused on long-term impacts for motor function, mental and emotional health, and adult life quality. Research also shows how sensory deprivation or altered environmental stimuli affect the neural wiring of adults through virtual and novel ecological realities. This includes adult onset myopia at university, smartphone-related onset of attention deficit hyperactivity, or age-related sensory and cognitive decline.

Mid-life deafness seems to be the highest risk factor for cognitive impairment and dementia in later life. One of the reasons is that hearing (and sight loss) lead to social isolation that allows for disuse-mediated degeneration of several cognitive functions and pathways related to neuropsychological wellbeing. Age-related deterioration of the vascular system is another aspect, which affects multiple cells and organs. Humans also have several sensory cell types that deteriorate with age in our ears, nose, and eyes. The organic rewiring that takes place after sensory loss in the brain is a natural response to supplement information losses and repair the situation, but the outcome is directed by cellular signalling, thus not a functional ideal. Think of it as a biochemical beureaucracy responding to an unforeseen emergency. Researchers at UC San Diego (McEvoy et al., 2023) recently discovered that after hearing loss, rewiring of cortical microstructures related to auditory processing and attention control may in fact be the mechanistic basis to development of dementia in these groups.

Here, it is worth pointing out that our auditory and visual sensory systems are closely integrated to aid in cognition, social communication, processing, and cue detection (See Zhang et al., 2022; Pennartz et al., 2023). This becomes another concern for patients with ocular diseases, as there seem to be auditory system consequences with adverse impacts on social functioning and communication. As such, frequently unemphasised are the more downstream consequence of high myopia and other sight-loss conditions are the 'psychological sequelae' (Demmin & Silverstein, 2020), neuronal network, sensory, and cognitive changes that follow. While less direct, this eye-brain + mental and social health perspective is an avenue for therapeutics that so far seems complementary to light-related lifestyles and preventive interventions for ocular health, individual longevity, and life quality. There is some hope that small changes to something like a spectral diet in dense urban territories will be able to tackle multiple links in the chain of civilisational public health problems.

### Ocular Pathology and Cognitive Alterations

Let's start with diabetic retinopathy (DR) as an example. DR as a result of diabetes is a major consequence of modern diets, but it is one of the few pathogenic pathway risks that *decreases* at higher levels of myopia. This seems to be due to axial elongation's effect on secretion of intraocular vascular endothelial growth factor (VEGF) and other cytokines, making it protective against DR severity (Kulshrestha et al., 2022).

Nevertheless, for cases that yield vision loss, there are social, emotional, and neurological consequences. Typically, visual impairment and vision-specific distress is associated with depression, anxiety, social withdrawal, and a cycle of mutually enforcing functional decline (Demmin & Silverstein, 2020). Another concept to note is that of 'neuroimmune crosstalk', which refers to how the central nervous and immune systems collaborate to deal with pathogenic and other challenges. DR studies provide a useful framework for approaching ocular-brain diseases that share degenerative mechanisms e.g. neurovascular problems, where type 2 diabetes is paired to manifestation of cognitive impairment and Alzheimer's.

Besides shared causes, as seen in some other forms of visual impairment Huang et al. (2020) describe 'large scale neuronal network dysfunction' in diabetic retinopathy, involving changes to structural (based on synaptic patterns and white matter tracts) and functional (time-based regional neural activation) connectivity. From the data, the study authors concluded that patients affected by DR had 'widespread deficits in both low-level perceptual and higher-order cognitive networks'. Another study cited in Ji et al. (2023) linked Type 2 diabetes to resulting dorsal attention network dysfunction and neurobehavioural defects.

Now in reverse: The inner retina and other ocular tissues reflect age-related neurodegenerative changes and disease of the central nervous system, and can be used as indicators of pathogenesis in conditions such as Alzheimer's, Parkinson's, and vascular cognitive impairment. As such, DR diagnostics can serve as a non-invasive proxy signal for dangerous cerebral abnormalities. In their review, K. Li et al. (2022) propose that pathogenic processes occurring for brain and eye disease are bidirectional, with the retina and central nervous system tightly wound via pre- and post-synaptic transmission. Studies cited indicate the possibility that changes to the posterior eye due to elongation in high myopia can be sent to and reflected in cortical networks and synaptic mapping.

Thalamic relay for the visual system is anatomically unique and a potential source of downward spiral-ly risk. For vision, it is thought that only 5 to 10% of the connections in the retina-thalamus-cortex pathway come from the retina. Beyond sensory information relay, this is instead a highly modulatory arrangement, with an estimated 80% of the connections in the lateral geniculate nucleus of the thalamus coming from the visual cortex, with other orders from various areas in the brainstem. This includes serotonergic, cholinergic, and adrenergic nuclei. Alterations to network function in the visual cortex can sometimes detrimentally feed back to the LGN, optic nerve, and retinal cells, or further into other parts of the brain.

On the 'extended visual system', one can refer to Pennartz et al. (2023), where sight is separated into the concepts of 'photic signalling' and 'vision', the latter being a conscious, perceptual phenomenon. This scope and approach may offer a better framework for if or how novel ecological environments and cultural mindsets could be affecting cellular processes in the mind and eyes. Precautionary note that the paper is based largely on rodent studies, where olfaction matters more for survival so there are a few differences in terms of sensory wiring.

## High Myopia

There are associations of myopia with emotional defects and cognitive impairment. For example, through mouse experiments Zhu et al. (2023) found that highly myopic stimuli led to anxiety and inflammation via upregulated expression of CC chemokine ligand 2 (CCL2) and monocytes in the eyes, additionally disrupting the blood-brain barrier. Presumably this has numerous consequences for adjacent synapses and circuitry, but it's complicated and experiments show mixed effects. On the positive side: CCL2 can be protective against apoptosis and excitotoxicity in the brain. Downside: Immune malfunction and associated molecules are now recognised as important underlying contributors to neuroinflammation and affective disorders like depression, with changes to synaptic firing patterns and structural connectivity another risk (See Curzytek & Leskiewicz, 2021).

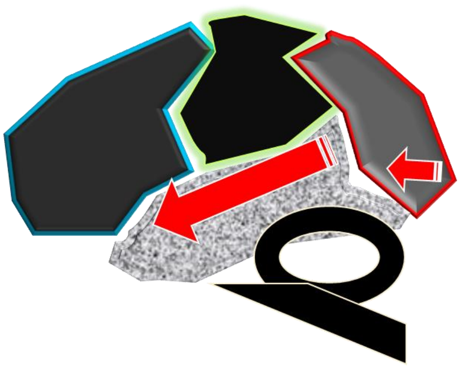
The resting state functional connectivity of high myopes (< -6.0 Dioptres, but with corrected visual acuity of better than 1.0) measured by magnetic resonance imaging (rs-fMRI) shows differences in brain activity versus healthy controls (Ji et al., 2022). One area affected was of course the visual network with reduced functional connectivity (FC) density. There were also changes to FC in auditory networks and regions, indicating auditory disorder, with similar occurring for the default mode network (DMN) to indicate cognitive abnormality. DMN1 (caudate nucleus, anterior cingulate gyrus) showed the most significant decrease in this study, and the increase in DMN-cerebellar network interconnectivity stood out, interpreted as motor and emotional disorder. The results differ quite a bit from another study done in 2016 by Zhai et al. Perhaps one influencing factor was that the latter cohort was composed of students at a medical university in Tianjin.

Prior research reviewed by Ji et al. (2022) indicated impacts to the frontal cortex, language comprehension, motor function, and attention and high myopia (also K. Li et al., 2022). Anatomical changes have also been found in terms of cortical thickness and gray matter volume in certain regions of the occipital cortex (cited in Ji et al., 2023).

The same group moved on to examine dynamic functional connectivity in high myopia patients, a measure of neural network adaptability (Ji et al., 2023). Areas where this 'significantly decreased' were concentrated in the occipital cortex: V1, the calcarine sulcus, and lingual gyrus, but the authors express some uncertainty about sliding window duration for their dynamic connectivity results. As such, it is unknown whether this feature of neural activity in high myopes actually represents an issue with 'visual information processing'. This is not restricted to the photic category of information, as the lingual gyrus is known for processing colour, faces, and symbolic data like letters and landmarks.

K. Li et al. (2022) discuss high myopia and cognitive impairment as an eye-brain disease, while suggesting the recent concept of a third visual pathway extending into the temporal lobe between the conventional dorsal (direction, motion) and ventral (object identifying) routes. This veers into the territory of the superior temporal sulcus, which is a region of heteromodal social interaction processing, with visual and vocal sensitive-voxels and audiovisual integration. The creep of pathology through various types of synaptic transmission and plasticity is hinted at here, to some extent indicated by Cheng et al. (2019)'s (cited in Li et al. 2022) comparison of healthy controls, low-moderate myopia, and high myopia brain activity. High myopia patients showed more differences in the amplitude of low-frequency fluctuations in bordering (outer cortical) brain regions compared to low-moderate myopia and healthy controls.

Given the role of the choroid in myopia, fMRI based on blood oxygenation level-dependent (BOLD) signals may be an additional tangent. It would be interesting to examine static and dynamic FC changes in tandem with patient vascular status and characteristics. There is an additional possibility that measured fMRI is a reflection of patient's myopia-associated scenery beyond the retina, as visually fractal environments can alter brain waves and DMN function.



*Four lobes of the brain. Arrows for visual cortex and superior temporal sulcus in third visual pathway described in K. Li et al. (2022). Occipital lobe dynamic connectivity affected by myopia (red border), parietal with dorsal attention* *network can be increased by green light (green border) and frontal cortex, where salience network activity is increased by blue light (blue-bound).*

**Communicating Retinal and Neurological Risks to Parents & Patients**

Consider all of the above and the seemingly growing global environmental risks of myopia onset and progression. How does one tell a parent/patient that myopia control is worth the investment for decades of ocular and neural health, and convince them to put time, effort, and money into prioritising lifestyle and clinical management of risk? Is bringing up the neural network changes, visions of bursting retinal tissue, and secondary blindness a good idea? They should probably be aware, but communication requires delicacy. People shouldn't be frightened into committing to an intervention, as exciting as it may be to present images from fractal analysis of neovascularisation in myopia-related retinal disease.

As is shown in rehabilitation techniques for vision impairment in older adults, promoting self-efficacy (Demmin & Silverstein, 2020) and a sense of personal power and agency over outcomes is a positive approach for managing disease and attendant psychological wellbeing. Practitioners can use research to explain why a particular lifestyle intervention, such as being outside amidst plants or adopting protective spectral hygiene habits is protective. Rather than staying indoors studying or scrolling, data snippets such as the effect of plants on cognition and academic achievement can be presented as tactics to improve grades. It's not ideal, but it's something.

Regarding cognitive functions, the meta-analyses further provided evidence synthesis that . . .

PARTICIPANTS EXPOSED TO INDOOR PLANTS HAD SIGNIFICANTLY HIGHER ACADEMIC ACHIEVEMENT THAN THEIR COUNTERPARTS

In Han et al., 2022

Clear instructions for use and importance of myopia management devices complete with mechanistic explanations could make a difference to compliance. Complacency matters and manifests not just in terms of therapeutic compliance, but deliberate mitigation of environmental risk. Often patients receiving a device or pharmacological intervention perceive it as a magic bullet that wards all problems and behavioural modification requirements away. However, we know the visual environment matters. Adopting little habits and lifestyle measures against myopia is comparatively cost-effective – a big selling point – particularly if computed over the long-term. Furthermore, small steps and habits implemented daily make a world of difference in terms of ocular-neural health and therapeutic outcomes. The most robust results we have so far in school-age myopia seem to be regular exposure to natural lights and sights and near work disruption (blink, take breaks, move gaze, sit at a distance) with reasonable suspicion as to the importance of sleep cycles and learning styles.

The most frightening results besides ocular diseases and secondary blindness are the considerations for neural health over time (e.g. in Ji et al., 2023). Sometimes people underestimate the importance of their sight over the next few decades, but snap to attention when told something could be negatively affecting their brains. Without being too graphic or alarming, this could be an additional angle for health communications that could modify behaviours, or legitimise greater public investment in greenery provision, salutogenic architecture, and alternative educational approaches. Use of LEDs might be intelligently adapted on this basis as well (See Campbell et al., 2023).

Another concern relates to increasing availability of self and home-use devices, comprising light therapeutics, apps, supplements, and poorly verified or explained internet-based advice. The possibility of doing harm through misuse, overuse, mis-timed use, or even underuse has to be made clear. Negative outcomes from a poor quality product or incorrectly implemented protocol undermine the data and attitudes towards valid therapeutics and interventions.

Our body serves a variety of complex functions and over-correcting in one aspect can compromise another, for example a trade-off between alertness for night time studying and sleep quality. Additionally, most biological processes are integrated with each other and the environment a species evolved in. Many pathways and mechanisms are still being uncovered at molecular and neural levels (for photobiomodulation examples, see Ramakrishnan et al., 2024). Altering a single input dimension when we don't *really* know all the factors involved can yield unforeseen biomedical and even behavioural consequences. It's good to try, but it's best to do so cautiously and sceptically.

**Conclusion**

Over the course of the article, you may have noticed that some of the colour, neural network, and myopia results seem contradictory. Myopia development remains a misunderstood and complicated process, and the variety of experimental designs at this stage significantly constrains the ability to draw definitive conclusions about cohorts, circuits, external causes, culpable molecules, and solutions. The aspects of animal model suitability, molecular complexity, and time window selection remain challenging, but it's looking up. Colour-focused research and introduction of organic visual content, with limitations of spectrally artificial light exposure seem promising. Incorporating contrast and finer spectral dimensions, then observing how changes to stimuli-specific sensory cells and neural circuits is leading to myopia, would be beneficial for research. This could then feed into virtual applications, e.g. fake audiovisual health-centric environments if we are too stubborn, cheap, or otherwise unable to make them a reality.

Given advances in neuroimaging and data analytics, it could be an opportune time to take our exploration of axial elongation culprits further back into the brain. Again in fact, as this theory fell out of favour some years prior, before several major advancements in computing and imaging technologies and cellular and systems neuroscience. Whether the research is to find out how neural activity affects or is affected by the novel technological/ecological forces behind mass myopia, findings may serve populations well in terms of cognitive longevity and ocular health.

None of that matters if we decide that becoming digitally-optimised and artificially-maintained jelly creatures is best and reconfigure our spaces, genetics, and developmental processes accordingly. That does seem metaphorically myopic, though. After all, the electricity still goes out. Further, we possess literary precautions such as 'Thus hath the candle singed the moth'. Yet unlike us, urban moths have genetically learned *not* to fly towards artificial lights (Altermatt & Ebert, 2016) and they don't even know what 'anthropocene trap' means. They probably can't even spell it.

There's a final consideration. A recent article in *BioEssays* proposed the 'longevity bottleneck hypothesis'. Basically, we have predatory dinosaurs to thank not just for night vision, then dying off so we can proceed in colour-sighted fruit-nibbling peace, but also the mammalian ageing process. The author suggests that the pressure for early mammals to survive and reproduce under 100 million years of dinosaurian dominion led to loss of longevity (DNA repair, regeneration, and lifelong reproduction) genes and pathways (De Magalhaes, 2023). Ageing itself is considered a 'detrimental phenotype' (Ibid.), and we are in a pretty unnatural situation where not just myopia but the number of elderly is expected to double by 2050 (In Ramakrishnan et al., 2024; Holden et al. 2016).

These projections are not just about the warping of demographic pyramids. They demonstrate that we require radical shifts in healthcare approach or capacity to handle the age-related, ocular, neurological, and psychological disease burden of modern civilisation. Yay for us, we have achieved this thanks to exploitation of our predator-free but tech-dominated ecological niche. However, our biologically grounded brain tissue and delicate retinas are still extremely vulnerable to ageing and light-mediated malfunction. As such, our bodies have the capacity to survive far past the onset of ocular disease and cognitive impairment due to cellular damage and senescence. This is a daunting public health burden for highly myopic ageing Asian populations.

Or…

Maybe amphibians and reptiles don't age as much because they don't think so much. The moral of the myopia story may be: Take a break, go outside, stare at nothing, don't worry. Eat fly. Lie in wait for drinking zebras. Sun yourself on a rock.

Wishing Everyone a Very Happy and Far-Sighted New Year.

**Disclaimer**: *The material presented is for informational and entertainment purposes only, in summary of recent news and events. It neither reflects the views nor constitutes professional advice of the organisation. The major sources used are referenced below.*

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