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Impact of light-emitting diodes on visual cortex layer 5 pyramidal neurons (V1-L5PNs)—A rodent study

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Purpose: Light-induced neural retinal insult leads to alterations in the visual cortex neurons. We examined light-induced neuronal alterations in the visual cortex layer 5 pyramidal neurons (V1-L5PNs) of adult male Wistar rats.
Methods: A total of 24 rats were divided into the following groups (n=6 each): control (NC), blue (BL), white (WL), and yellow (YL). The exposure groups were subjected to light-emitting diodes (LED) exposure (450–500 lx) of differing wavelengths for 90 days (12:12 16 light–dark cycle). After LED exposure, the animals were sacrificed, and the brain tissues were removed and impregnated in freshly prepared Golgi–Cox stain for 21 days. Sholl's grading analysis was used to quantify the apical and basal dendritic branching points and intersections of the V1-L5PNs.
Results: There was a significant difference in the number of apical branching points among all groups ($p<0.001$), with a particularly notable difference between the BL and WL groups ($p<0.001$). A post hoc test revealed that all exposure groups (BL, WL, and YL) had fewer apical branching points ($p<0.001$) on an average of 3.6 µm and a significant reduction in the dendritic intersections ($p<0.001$) compared to the number of branching points extending from layer Va (V1) neurons.
Conclusions: Chronic and cumulative exposure to blue and white LEDs led to the pruning of V1-L5PNs, which might impair visual processing.

In mammals, visual performance and potential well being are determined by the different types of light exposure. Artificial light, whose properties differ from natural light, continues to increase in prevalence in our visual environment. Despite its advantages, narrow-band light sources pose potential hazards. A high proportion of high-energy short-wavelength (blue) visible light can potentially harm the visual system [1], causing retinal injury and visual dysfunction [2–5].

The impact of blue wavelengths on the visual system has gained research interest in recent years, especially due to the increased use of digital devices. Light-emitting diodes (LEDs) emit a high proportion of high-energy short-wavelength light [2–4], with an emission peak at a blue wavelength (400–455 nm) [5–7]. Cumulative exposure to blue light has been associated with eye strain in humans [8,9]. Retinal light toxicity can present as photooxidative stress [10], photomechanical damage, or photochemical damage [11–13], eventually leading to the loss of photoreceptors [14–16], retinal pigmented epithelium (RPECs) cells [17,18], and retinal ganglion cells (RGCs). The activation of Müller cells and microglia is consistent with an inflammatory stress response [19], which is related to the excessive production of reactive oxygen species (ROS), reduced bioavailability of nitric oxide [6], and subsequent neuronal injury [20].

In addition to retinal injury [7], excessive blue light exposure can impact the non-image-forming functions of the visual system, including circadian entrainment [21–23]. In particular, light injury to intrinsically photosensitive retinal ganglion cells (ipRGCs) impacts the master clock, which is the suprachiasmatic nucleus (SCN) in the hypothalamus responsible for regulating non-image-forming functions [24,25]. Numerous studies have demonstrated the impact of LED exposure on a range of ipRGC targets in the brain [17]. However, fewer studies have compared the impact of chronic short- and long-wavelength LED exposure on visual cortex neurons. Hence, this study aimed to morphometrically analyze V1-L5PNs following prolonged exposure to LEDs of differing wavelengths.

METHODS

Ethical approval: This study received approval from the Institution Research Committee (IRC) and Institutional Animal Ethics Committee (IAEC; IAEC/02/2017), Manipal Academy of Higher Education, MAHE, Manipal. Following approval, 24 healthy adult male Wistar rats were procured from the Central Animal Research Facility (CARF), MAHE, Manipal, and maintained under the guidance of the Committee for

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the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Laboratory and lighting setup:

Control animals—The control (NC, n=6) animals were maintained in the laboratory under normal room lighting conditions, which were provided by fluorescent lamps (Kfin Technologies Limited, TL5 Essential HE Super 80, Unit: Signify Innovations India Limited) placed at a 3.05 m distance from the animals, offering 250–300 lx. The light sources were turned off during the daytime to maintain the animals' circadian rhythms.

Experimental animals—The animals were divided into three experimental groups (n=6 per group) and a control group (NC, n=6). The animals in the experimental groups were exposed to blue (BL, n=6), white (WL, n=6), and yellow (YL, n=6) LEDs. Throughout the experiment, the animals in the different exposure groups were kept on a 12:12 h light–dark cycle, with light exposure at night from 9:00 PM to 9:00 AM The light source used was a cumulative LED lighting system that provided an average illumination level of 400–500 lx.

The animals were housed in individual cages (length=100 cm, width=70 cm, and height=50 cm). The spectral characteristics of the LEDs measured using a spectrometer (Lighting Passport Pro, Taiwan) were as follows: blue (400–490 nm), white (380–780 nm), and yellow (400–780 nm) LEDs, as shown in Figure 1. The LEDs were fitted at a height of 50 cm from the cage floor, considering the rats' anatomic eye position. After being adapted to laboratory conditions for a week, the animals were exposed to LED light. The illumination levels were calculated vertically and horizontally and then averaged to ensure consistent and reliable results. The light output was measured from the bottom of the cage. Following 90 days of exposure, the animals were sacrificed with a lethal dose of pentobarbital (i.p. 100 mg/kg) and xylazine (10 mg/kg), and brain tissue was harvested and impregnated in freshly prepared Golgi–Cox solution.

Visual cortex Golgi impregnation technique: The Golgi–Cox fixative included potassium chromate (Spectrum Reagents and Chemicals Pvt. Ltd., Edayar, Kerala, India), mercury chloride (Medilise Chemicals, KRL/KNR/00087/2003, Azhikode Kannur, Kerala, India), and potassium dichromate (Spectrum Reagents and Chemicals Pvt. Ltd., Edayar,). The solution was replaced every five days until 21 days to maximize penetration and ensure uniform staining. At the end of the impregnation period, one hemisphere of the brain was fixed to a sledge microtome plate (Radical Scientific Equipment, Pvt. Ltd., Ambala Cannt, Haryana, India) with one drop of quick fix glue (PELCO Pro CA44 Tissue Adhesive, Ted Pella Inc., Fisher Scientific Lab), and sections (150 µm) were acquired and transferred to tissue cassettes (Leica-LP-C biopsy cassettes, Leica Biosystems, India Pvt, Ltd.) for

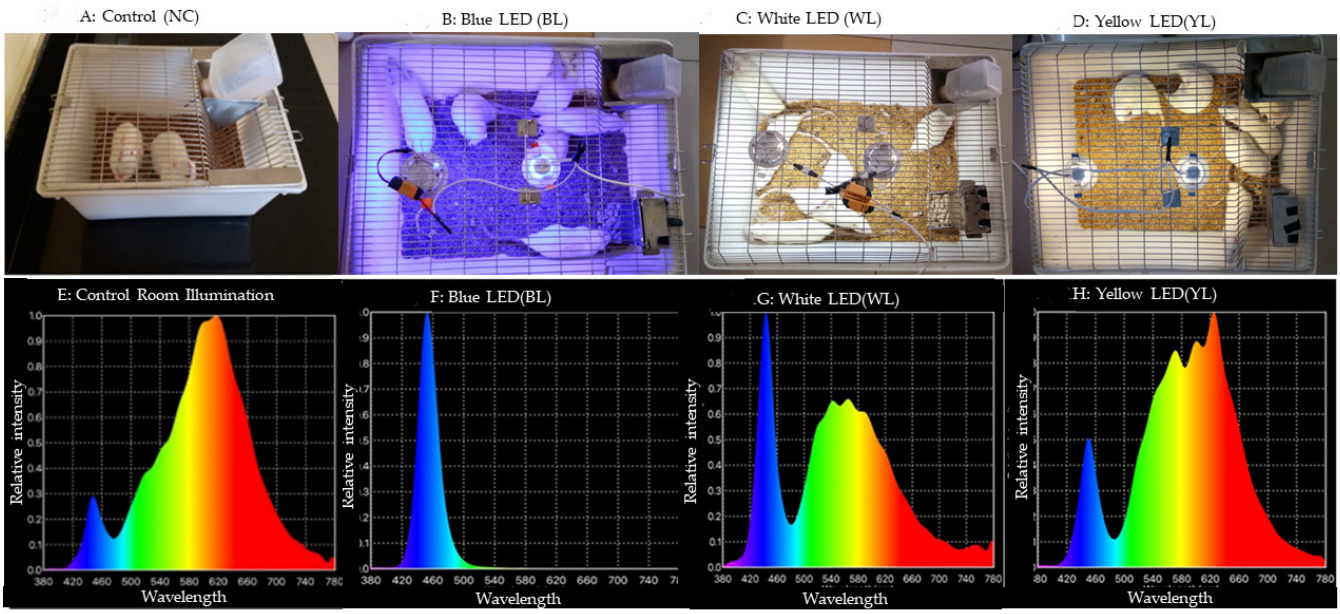

Figure 1. Different animal groups and their respective light conditions. **A**, **E**: Control animals and room illumination. **B**, **F**: blue light; **C**, **G**: white LED; and **D**, **H**: yellow light. The x-axis shows the wavelength, and the y-axis shows the relative intensity of the transmitted light.

immersion in 5% sodium carbonate solution (Sigma-Aldrich, Darmstadt, Germany) for 20 min. Following this, the tissue sections underwent dehydration in different concentrations of 70% (2 washes), 90% (2 washes), and 99.9% (3 washes) for a period of 10 min in each wash of ethyl alcohol (Ethanol, UN No.: 1170). As a final step, the tissue sections were made transparent with a wash in sulfur-free xylene (Spectrum, New Brunswick, NJ).

Tissue processing, dehydration, and mounting: The tissue processing and staining protocol was adapted from our previous similar experiment [26]. Neurons were selected carefully at the border of layer 4 to distinguish layer Va from layer Vb of the primary visual cortex (V1) due to the increase in cell density in layer 4. In contrast, the boundary between layers 5 and 4 is less precise [27]. A total of 864 neurons (NC: 36*6=216, BL: 36*6=216, WL: 36*6=216, and YL: 36*6=216 neurons) were selected from V1-L5PNs from each group. Two investigators manually traced dendrites from the coded slides and tabulated the pooled mean values for each group. The number of branching points and intersections in relation to the apical and basal dendrites of neurons was quantified using Sholl's circle, starting with 20 µm concentric circles up to 140 µm from the soma. We traced up to 140 µm concentric circles because in the V1-L5PNs, the dendritic arbors can extend up to 220 and 240 µm in Sholl's analysis. There was an abrupt decrease in segment lengths and diameters for terminal arbor segments beyond 150 µm [28]. The mean of the acquired data was compared across all groups.

Statistical analysis: Statistical analysis was performed using R software (version 3.6.3) [29]. A two-way ANOVA (ANOVA) was used to compare the differences in visual cortex pyramidal neurons, and Tukey's honest significant difference (HSD) post hoc test was used to determine differences between groups, if any.

RESULTS

Light-induced neuronal reprogramming: Golgi-stained morphometric analysis suggested a paucity of distinct V1-L5PNs in the BL and WL exposure groups but not in the NC and YL groups at the end of the 90-day exposure period. The BL and WL groups demonstrated an altered dendritic morphology, resulting in fewer dendritic branching points from the soma, an effect evident in all light exposure groups (Figure 2). There was a significant difference p eg F18, F126; $p < 0.001$ in the apical branching points across all groups as a function of distance from the soma (Figure 3), according to the results of two-way ANOVA. However, there was a significant difference between the BL and WL groups p eg F18, F126; $p < 0.001$. The post hoc comparison of the main effects showed that all light exposure groups (BL, WL, and YL) had fewer apical branching points than the NC group.

The comparison of basal branching points revealed a significant difference between the NC and BL groups at the 0–20 µm and 20–40 µm distances, and the branching points slowly declined from 40 to 140 µm in the BL group (Figure 3B). Both the BL and WL groups showed fewer branching points (1.89 µm) at a distance of <60 µm from the soma, although a similar number of branching points was found from the soma. Two-way ANOVA revealed a significant difference between the light exposure groups ($F_{18,126}=2.07$, $p=0.012$). Multiple comparisons of light exposure groups showed fewer basal branching points in the BL, WL, and YL groups compared to the NC group ($p<0.001$). However, there was a significant difference between the NC ($p<0.05$) and YL, BL, and WL ($p<0.001$) groups.

Regarding the number of apical dendritic intersections (Figure 3C), there was a significant difference across all the groups ($F_{3,40}=0.25$, $p<0.0001$). Post hoc analysis revealed that the BL and WL ($p<0.001$) and YL ($p<0.0001$) groups demonstrated significantly lower intersections (1.96 µm) compared to the NC group (5.89 µm).

DISCUSSION

Our main finding was alterations in the morphometry of L5PNs in the primary visual cortex, specifically decreased dendritic branching points and dendritic intersections in the BL and WL exposure groups. These outcomes are moderately associated with the stated hypothesis. Visual cortex activity relies on the robustness of RGCs [30]. Shang et al. showed that continuous exposure to white LEDs can lead to damage in RGCs [4,6,7], leading to retrograde damage in visual cortex neurons [31,32]. An alteration in the morphology of neurons in the visual cortex is consistent with a reduction in RGCs apoptotic caspase-3 immunostaining, as shown in our recently published article [6,26]. Alterations in V1-L5PNs' basal dendritic branching points and intersections occur when the retina is bruised and injured, including as a result of ischemic retinal degeneration and glaucoma [33–38].

Damage to ganglion cell axons can lead to retrograde degenerative changes and apoptosis of RGCs, as well as the death of anterograde transport cells and Wallerian degeneration, which in turn impact various sites of RGC termination in the brain [31]. Evidence suggests that deterioration of the retinal nerve fiber layer (RNFL) and RGCs is associated with degeneration, leading to the degrading of the visual processing [39,40], and eventually leading to trans-synaptic degeneration [40].

Compared to classical photoreceptors, ipRGCs are most sensitive to a wavelength of approximately 482 nm [41]. Photoreceptors receive light from an external source and serve as neural signals. They stimulate the ipRGCs and send their projections to the SCN via the retinohypothalamic tract. Hence, damage to the RGCs as a result of blue and white LED exposure could have triggered morphometric alterations in the V1-L5PNs. Constant and cumulative light exposure damages RGCs [6,26], further damaging pyramidal neurons in the visual cortex [26] and hippocampal neurons (CA1 and CA3) [42].

The BL and WL groups showed a significantly reduced neuron population of V1-L5PNs. Specifically, the YL group showed increased basal branching points and intersections compared to the BL and WL groups. This could have been due to excessive RGC damage as a result of blue and white LED exposure compared to yellow LED exposure [6,7]. V1-L5PNs are responsible for firing properties in the visual cortex region from the molecular to the multicellular layer [43–45]. Changes in V1-L5PNs' dendritic branching points and intersections in BL and WL groups could potentially deprive the visual stimuli of different downstream targets, especially higher-order visual areas, inhibiting spatial and temporal information. Maximum retinal degeneration occurred at 450 nm within the blue wavelength, meaning that the blue wavelength might affect proto-oncogene expression in the paraventricular nucleus in the hypothalamus and the low expression level of c-Fos under the organic LED (OLED) condition [46]. Therefore, neurons projecting to V1 areas require higher selectivity in terms of visual features and functions. In contrast, the loss of dendritic branches in the BL and WL groups might have altered neural circuits and chemical messenger interactions in the visual cortex area.

However, this study has a few limitations, such as a lack of functional measurements using an electroretinogram (ERG) and the failure to map retinal changes along with

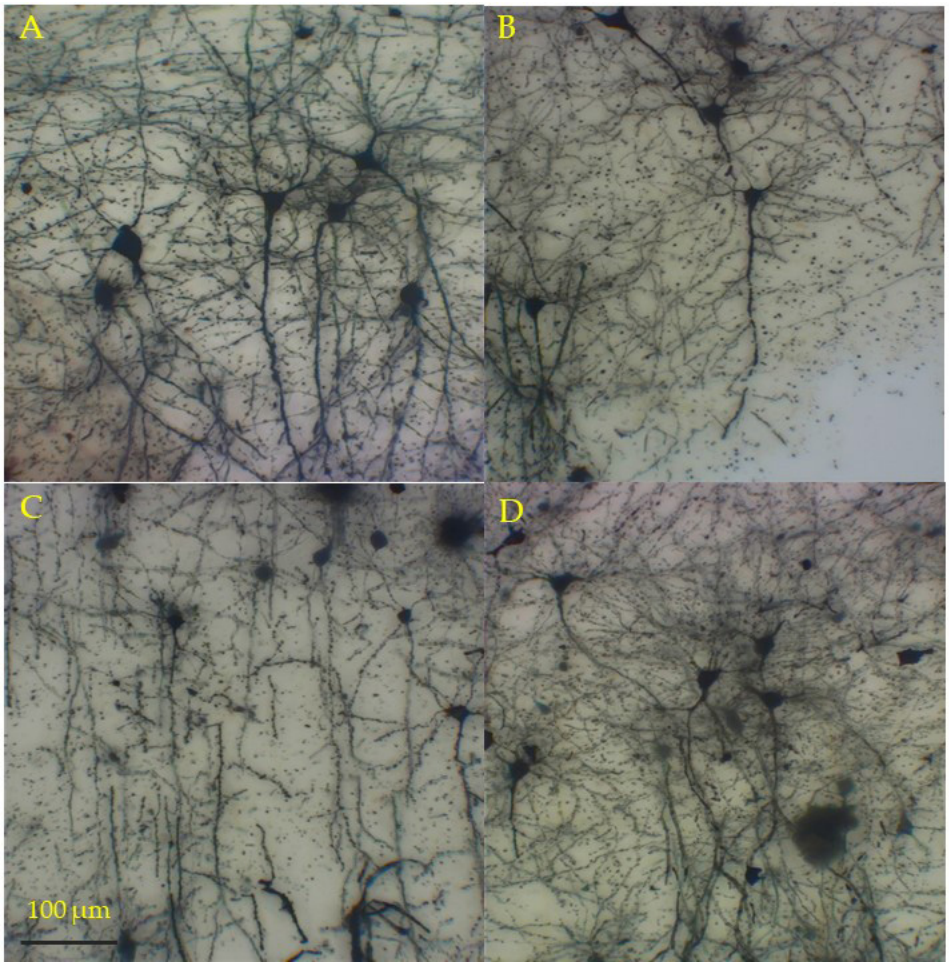

Figure 2. Golgi-stained V1-L5PNs. Golgi-stained V1-L5PNs obtained from four groups: control (**A**), blue light exposure (**B**, BL), white light exposure (**C**, WL), and yellow light exposure (**D**, YL). The images are accompanied by a 100 µm scale bar.

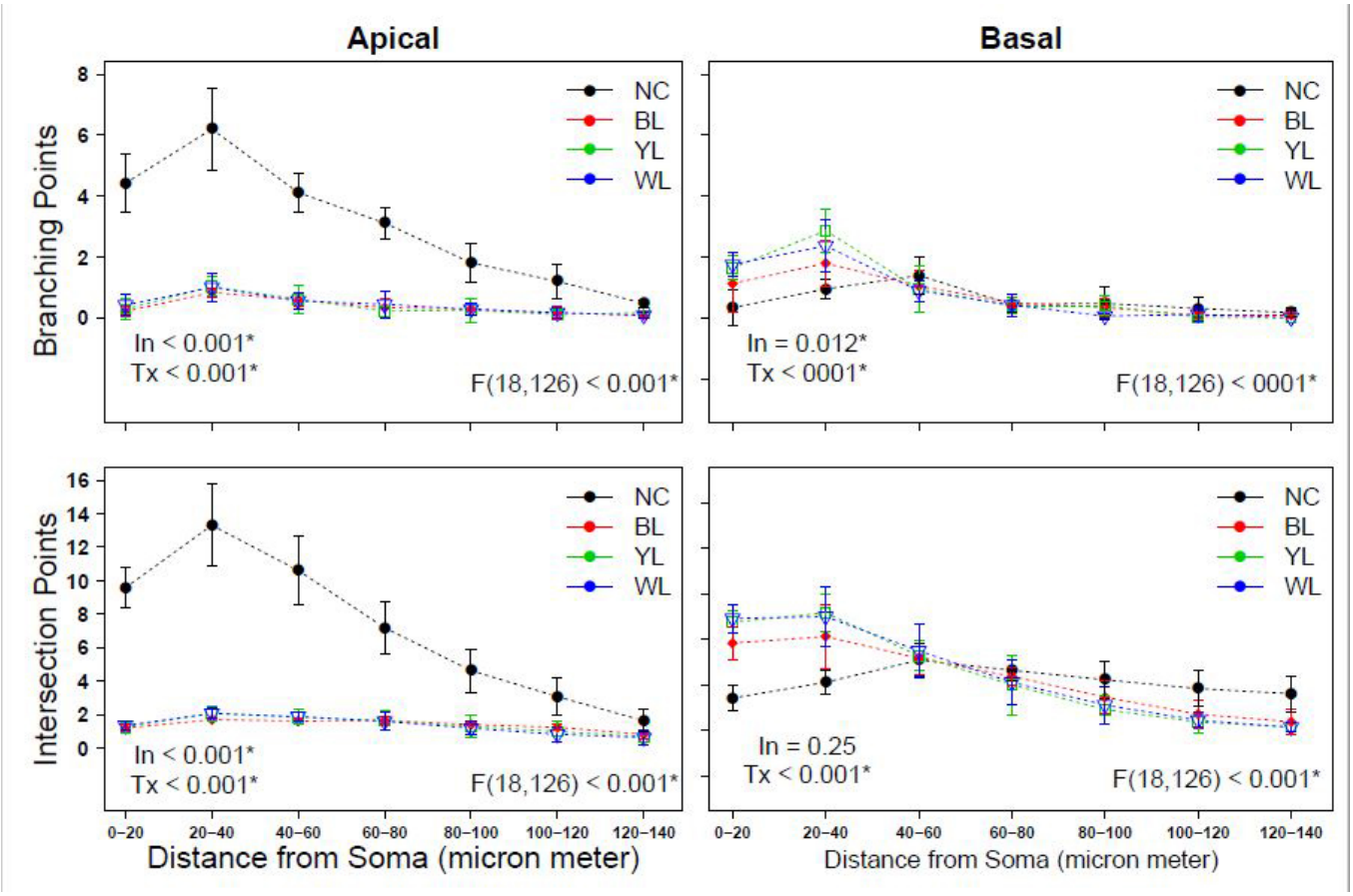

Figure 3. Four groups. Four groups (NC=control, BL=blue light exposure, WL=white light exposure, YL=yellow light exposure) and their corresponding number of apical and basal dendritic branching points, as well as apical and basal dendritic intersections at different distances from the cell soma. The error bar indicates the standard error of the mean. The p value for the interaction between group and distance (In) and the difference across the groups were derived from a two-way ANOVA.

cortical alterations to understand the impact of prolonged light exposure. In addition, due to technical constraints, we could not measure the degree of light absorption by the photoreceptor. This limitation prevented us from gaining a more comprehensive understanding of the photochemical and thermal damage associated with visual cortex neuronal pruning.

Conclusion: Prolonged and cumulative exposure to white and blue light causes apparent neuronal loss and pruning of neurons in the visual cortex of rodents, while this damage is minimal with yellow light exposure.

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