The Antidepressant Effect of Light Therapy from Retinal Projections

Review

The Antidepressant Effect of Light Therapy from Retinal Projections

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Abstract:

Observations from clinical trials have frequently demonstrated that light therapy can be an effective therapy for seasonal and non-seasonal major depression. Despite the fact that light therapy is known to have several advantages over antidepressant drugs like a low cost, minimal side-effects, and fast onset of therapeutic effect, the mechanism underlying light therapy remains unclear. So far, it is known that light therapy modulates mood states and cognitive functions, involving circadian and non-circadian pathways from retinas into brain. In this review, we discuss the therapeutic effect of light on major depression and its relationship to direct retinal projections in the brain. We finally emphasize the function of the retino-raphe projection in modulating serotonin activity, which probably underlies the antidepressant effect of light therapy for depression.

Keywords: light therapy, depression, retinal projection, serotonin, opsin

Introduction

Light, a type of energy originally from the sun, affects our mood and cognitive function [1, 2]. The retina, part of the central nervous system, has a uniquely photosensitive function [3, 4]. Light effects on mood and cognition are most likely to act through retinal circuitry and its retinofugal projections into the brain. Notably, bright light therapy appears to be a promising treatment for major depression, due to the rapid onset of benefit, minor side-effects, and low cost [5, 6]. As early as the 1980s, several clinical reports already indicated that light therapy alone is effective in treating depressive disorders [7, 8], which currently affect ~298 million people and are a leading cause of functional disability worldwide [9]. Major depression often leads to enormous personal suffering, financial costs, and an imposing social burden [10–12]. The pathophysiology of depression is still unclear but is proposed to interact with genetic and environmental factors [13]. The complexity and heterogeneity of depression have largely hampered its diagnosis and treatment [14]. Currently available antidepressants, such as selective serotonin reuptake inhibitors (SSRI) , mainly exert their therapeutic effects *via* reducing serotonin (5-HT) turnover in the brain [15]. However, the delayed treatment effect (weeks to months) and relatively low response rate are thought to be associated with the high rate of suicide in depressed patients [14]. Other side-effects include significant weight gain and sexual dysfunction [16].

Here, we review the therapeutic effect of light therapy on depression in clinical trials and preclinical studies, and discuss the possible neural circuitry of light-signal input from retinas to brain regions, as well as their roles as potential pathways underlying light therapy for major depression.

Light Therapy for Depression in Clinical Trials

Clinical reports (Table 1) have shown, for example, that drug-free patients with major depression treated with bright light for several hours each day for a week show a significant decrease in depression ratings in comparison to patients treated with a dim red light placebo [17]. Kripke concluded that the net benefits of light therapy for major depression are similar to those resulting from antidepressant drugs including fluoxetine, sertraline, and imipramine; and the efficacy of light therapy is equal in treating seasonal and non-seasonal depression [6]. During the last three decades, however, light therapy has mainly been used to treat seasonal affective disorder (SAD) patients; this might be due to the phenomenon that light therapy seems to benefit winter depression more because of a circadian phase shift with the light stimuli [18, 19]. Emerging evidence from clinical trials using double-blind, placebo-controlled, and randomized standards has recently demonstrated that light therapy is effective in treating non-seasonal depression as well [5]. Significant efficacy of light therapy has been reported in a study using 89 elderly patients with non-seasonal major depressive disorder (MDD) when compared to randomized placebo controls [20]. Furthermore, bright light therapy as a monotherapy has been demonstrated to have a beneficial effect on 28 adolescents with non-seasonal depression [21].

Table 1 Light therapy for seasonal and non-seasonal depression.

Group	Light source	Wavelength	Illuminance	Time	Efficacy	Ref.
28 adolescents aged 14-17 years with mild MDD	Bright light box	White light	2,500 lux *vs* 50 lux	1 week of 2,500 lux 1 h/day	Significant differences between treatment and placebo	Niederhofer *et al.*, 2012 [21]

					groups	
89 outpatients with MDD ≥60 years old, 47 randomized as control	Fluorescent tubes (Philips, HF 3304)	Pale blue in white light *vs* dim red light	White light at 7,500 lux *vs* red at 50 lux	1 h/day, early morning, 3 weeks	Improved mood, sleep efficiency, and increased melatonin gradient	Lieverse *et al.*, 2011[20]
27 pregnant women with non-seasonal MDD, 11 randomized as control	Fluorescent bright white light	Bright white light	White light at 7,000 lux *vs* red light at 70 lux	1 h/day, at home, in morning after waking, 5 weeks	Significant improvement during pregnancy, no known risk for mother and unborn child	Wirz-Justice *et al.*, 2011 [23]
18 outpatients with SAD aged 18-64 years, *n* = 9 each group	LED (goLITE ®)	Blue light, 464 ± 27 nm *vs* blue-enriched white light, 400-700 nm	Blue light at 98 lux *vs* white light at 711 lux	45 min/day, in morning after waking, 3 weeks	Equal effects	Anderson *et al.*, 2009 [132]
30 individuals with SAD, 13 randomized as control	Provided by sponsor	Blue light, 470 nm *vs* red light, 650 nm	Blue light at 176 lux *vs* red light at 201 lux	45 min daily at 06:00-08:00 am. 3 weeks	Blue light superior to red light	Strong *et al.*, 2009 [133]

26 SAD patients aged 18-65 years, 11 randomized as control	LED (Liteboo k)	White light with spectral emission peaks at 464 nm and 564 nm	White at 1,350 lux	0.5 h/day, before 08:00 am, 4 weeks	Proportion of patients in remission significantly greater (SIGH-SAD <9).	Desan *et al.*, 2007 [134]
158 patients with SAD aged 18-65 years, randomized into 6 groups	SPX-30 triphosph or fluoresce nt lamp (Hughes Lighting Tech)	High intensity white light *vs* negative air ionizer	White at 10,000 lux	30 min/day, 10-14 days	Better response to morning than evening light	Terman *et al.*, 1998 [18]
51 drug-free in-patients with non-seasonal MDD, 26 randomized as control	Bright white light device (unknow n)	Bright white light *vs* dim red light	White light at 2,000-3,000 lux *vs* dim red light	1 week	Difference in global depression score (P = 0.02).	Kripke *et al.*, 1992 [17]

MDD, major depressive disorder; SAD, seasonal affective disorder or winter depression; LED, light-emitting diode.

Although clinical cases display various remission rates gained from light therapy, mainly using different light parameters, bright light therapy has already begun to show good prospects in clinical application for many depression disorders [5, 22], including winter depression [18], antepartum depression [23], treatment-resistant depression [22], and bipolar

depression [24]. Accumulating evidence has shown that light therapy is able to modulate mood state and cognitive function through circadian or non-circadian pathways [2, 25]. However, the mechanism underlying the effect of light therapy remains largely unknown [5].

Animal Studies on the Mechanism Underlying Light Therapy

In order to reveal the mechanism involved in light therapy, it has been used in animal models [5]. Iyilikci *et al.* reported that 1300 lux exposure to blue or white light for 10 min at zeitgebers time of 21:00 results in a significantly reduced immobility time of male Wistar rats in the second swim test relative to that of the first swim test [26]. However, that is just an acute model without any common stressors to activate a depression-like response, so the antidepressant effect was temporary but not sustained. A short photoperiod has also frequently been demonstrated to induce depression in rodents, usually that is seasonal depression [27, 28], so it was effectively rescued by light therapy [29, 30]. It has also been reported that chronic constant light (L/L cycle, 100–120 lux) for 3 weeks reverses the depressive-like response in a Sprague-Dawley rat model caused by maternal separation [31]. Nevertheless, opposite results have been obtained by Nelson and colleagues using light exposure at night. They revealed that dim light (5 lux) at night running for 3-8 weeks induced depressive-like responses in nocturnal and diurnal rodents [32], including hamster [33], Nile grass rat [34], and C3H/HeNHsd mice [35]. And the aberrant light condition also disrupted normal circadian rhythms and led to impairment of mood and learning [36].

Since the therapeutic effect of light therapy is clear in the clinical trials, the animal studies have been relatively limited. Thus, more profound and convincing studies to reveal the mechanism underlying light therapy are still needed.

Neural Circuitry from Retinas to Brain Involved in Light Therapy

Key Structures of Retinal Circuitry

The vertebrate retina is mainly composed of three layers of neuronal somata, with two layers of synapses (Fig. 1). The outer nuclear layer contains the somata of the photoreceptors (rods and cones). The rodent retina usually contains one type of rod and two types of cone photoreceptors that are sensitive to light with short and long

wavelengths, respectively. However, the primate retina has three types of cone: short, medium, and long cones. The inner nuclear layer contains the somata of the vertically-oriented bipolar cells, along with horizontal cells and amacrine cells. The ganglion cell layer harbors the somata of retinal ganglion cells (RGCs) and some displaced amacrine cells as well. These three neuronal layers are generally divided by two neuropils, in which synaptic interactions occur at crossed dendrites. The first neuropil is the outer plexiform layer where connections form between rods, cones, bipolar cells, and horizontal cells. The second neuropil is the inner plexiform layer, which functions as a relay station for carrying information vertically, mainly from the bipolar cells to the ganglion cells. In addition, amacrine cells interact in further networks to influence and integrate the signals of ganglion cells. Finally, RGCs project into the brain *via* their retinofugal axons [37].

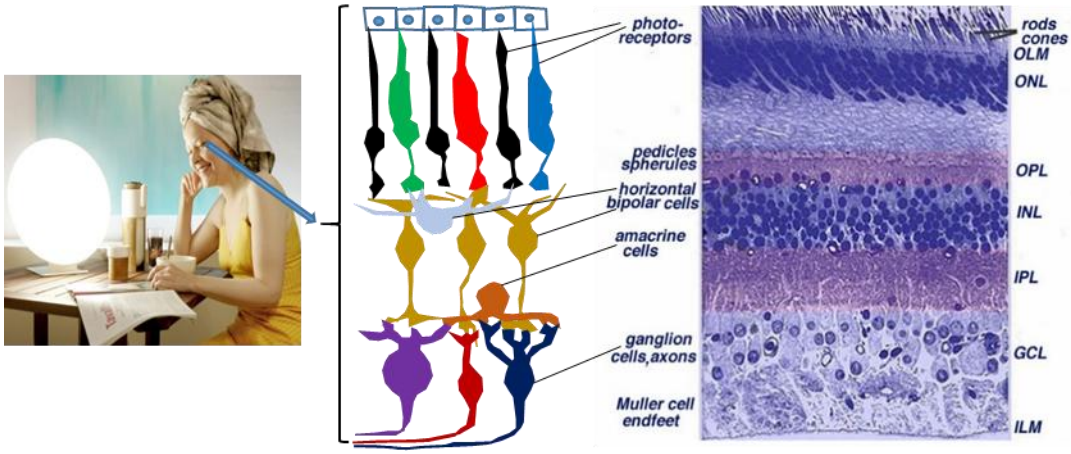

Fig. 1 Bright light therapy and the basic structure of the retina. A A lady conducting bright white light therapy in the morning (http://www.sad-lighthire.co.uk/images/gallery/256.jpg). **B** and **C** Cartoon and cross-section showing retinal structure: photoreceptors are rods and cones. The nuclei of bipolar cells are located in the INL, and retinal ganglion cells reside in the GCL, sending light signals through their axon projections into the brain. In addition, horizontal cells, amacrine cells, and Müller cells participate in the neuronal circuitry in the retina [3]. OLM, outer limiting membrane; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer; ILM, inner limiting membrane.

Retinofugal Projections from Retinas to Brain Involved in Light Therapy

RGCs extend their axons across the inner surface of the retina in the nerve fiber layer, and then exit the eye *via* the optic nerve head. These axons subsequently pass along the optic nerves to the optic chiasma. They intermingle there and sort to form the two optic tracts. Finally, the axons reach their respective terminals in target nuclei [38] . In the mammalian brain (Fig. 2), ~20 nuclei receive retinal projections. For example, the lateral geniculate nucleus (LGN) is a relay to the visual cortex, the superior colliculus (SC) is responsible for visual sensory-motor processing, and the hypothalamus is mainly involved in hormone balance. Many visual target nuclei are more likely associated with mood regulation, in particular, the amygdala (Amy), bed nucleus of the stria terminalis (BNST), lateral habenula (LHb), suprachiasmatic nucleus (SCN), and dorsal raphe nucleus (DRN). Light therapy for major depression probably involves these nuclei. Some, but not all, of these nuclei are illustrated in Figure 2.

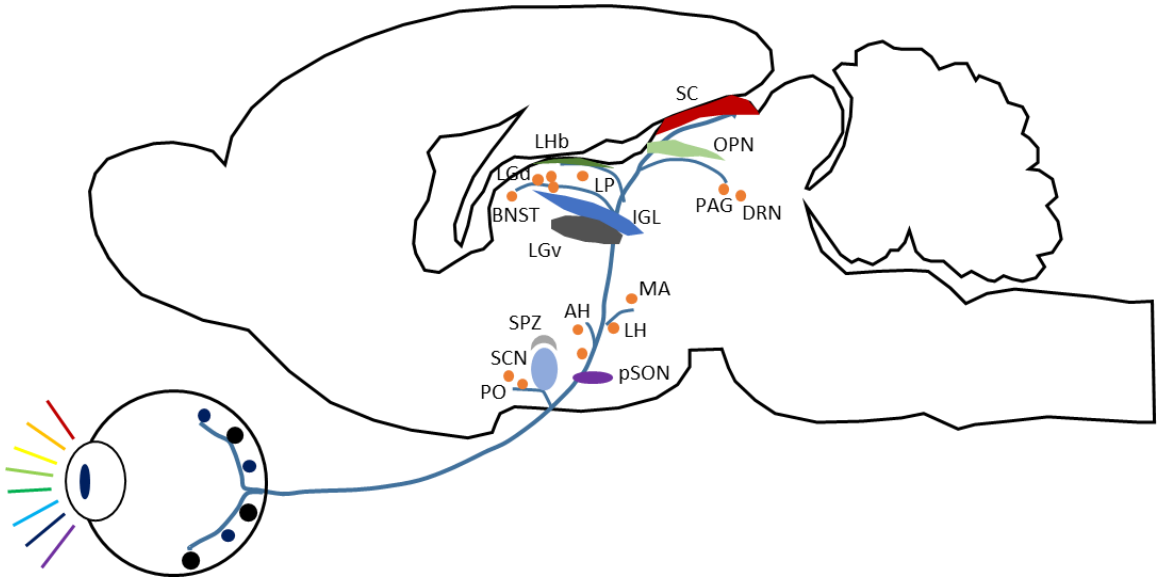

Fig. 2 Main retinofugal projections in the mammalian brain. Schematic of the main visual targets in the mammalian brain, based on rodent anatomy, mainly from Hattar *et al.*, 2006 [59]. The visual targets are retinofugal but not necessarily from intrinsically photosensitive retinal ganglion cells (ipRGCs) [115]. AH, anterior hypothalamic nucleus; BNST, bed nucleus of the stria terminalis; DRN, dorsal raphe nucleus; IGL, intergeniculate leaflet; LGd, dorsal lateral geniculate nucleus; LGv, ventral lateral geniculate nucleus; LH, lateral hypothalamic area; LHb, lateral habenula, LP: lateral

posterior thalamic nucleus; MA, medial amygdaloid nucleus; OPN, olivary pretectal nucleus; PAG, periaqueductal gray; PO, preoptic nucleus; pSON, peri-supraoptic nucleus; SC, superior colliculus; SCN, suprachiasmatic nucleus; SPZ, subparaventricular zone.

Suprachiasmatic Nucleus (SCN)

The SCN is the principal circadian pacemaker and is located in the anterior part of the hypothalamus, above the optic chiasma [39]. As the master pacemaker for circadian rhythms, the SCN is essential for the resetting of the circadian phase by light and the photic regulation of pineal melatonin synthesis. The projection from the retinas into the SCN is dominated by intrinsically photosensitive retinal ganglion cells (ipRGCs) containing melanopsin [40]. Almost all (>99%) of the RGCs projecting to the SCN express melanopsin in mice [40, 41], while 80-90% of the RGCs projecting to the SCN are melanopsin-expressing ipRGCs in the rat [42] and golden hamster [43, 44]. Monocular labeling of the retinal projection is often bilaterally symmetrical in the SCN, at least in mice [45], golden hamsters [46], and macaque monkeys [47]; this differs from other main retinofugal targets such as the LGN and SC that receive more contralateral projections [48]. It is still not clear that disruption of SCN directly results in mood disorders [49], since only limited evidence shows involvement of the SCN in mood regulation [50]. And bilateral lesions of the SCN in rats has been shown to reduce depression-like behavior in the forced swim test [51]. In a postmortem study, however, an increase of arginine vasopressin (AVP) neurons along with a decrease of AVP mRNA has been reported in the SCN of depressive patients [52]. Of note, other brain regions, such as the hippocampus and lateral habenula form many connections with the SCN [53, 54]. It is reasonable to speculate that the light effect on mood regulation may be partly due to modulation of the neural activity in the SCN [36], though it is not the only brain region linking the light response to mood regulation [55].

Amygdala (Amy)

The Amy receives relatively sparse retinal input compared with the SCN. A retinal projection into the Amy, mainly in the medial Amy, has been reported in the primate [56], hamster [57], rat [58], mouse [59, 60] and Nile grass rat [61]. The Amy is mainly implicated in

the regulation of emotion, especially the formation and storage of fear memory [62-64]. Fear conditioning is a key role of the Amy, linking external stimuli to defense responses [65]. Since chronic fear induces anxiety and depression, it is reasonable that Amy dysfunction has often been associated with anxiety and depression in humans [66-68], as well as in animal models [69-71]. Using optogenetic tools, a fine connection between the basolateral Amy and the central nucleus of the Amy has been implicated as a critical neural circuit for controlling acute anxiety in mice [72], and might be involved in major depression.

Bed Nucleus of the Stria Terminalis (BNST)

Retinal fiber innervation of the BNST has been observed in several species, including the primate [73], hamster [57, 74], rat [58], *Spalax* (blind mole rat) [75], mouse [48], and Nile grass rat [61]. The BNST in rodents and humans has been suggested to be involved in anxiety-related processes [76, 77], as well as in modulation of the hypothalamo-pituitary-adrenal (HPA) axis in response to stress [78]. The posterior BNST plays an inhibitory role in the HPA axis, while the anteroventral BNST is involved in its excitation [78]. And involvement of the HPA axis in depression is often regarded to act through hippocampal neurogenesis [79].

Animal studies on the pathophysiology of depression have focused on the BNST, but controversial results have been reported by different groups. Chemical inactivation of the BNST using cobalt chloride has been reported to have an antidepressant-like effect in rats *via* the forced swim test [80, 81], while bilateral electrolytic lesions of the BNST induces depression-like responses in male and female rats [82-84]. It is likely that the BNST plays bidirectional roles through its glutamatergic and GABAergic fibers to modulate stress-anxiety and depression [76, 85], respectively.

Lateral Habenula (LHb)

The LHb is a key nucleus mediating communication between the forebrain and midbrain [86]. It also couples with the serotonergic system at the raphe nucleus [86, 87], and the dopaminergic system in the ventral tegmental area [88]. The LHb has been reported to contain a direct retinal projection by several groups. The first report of a retino-LHb projection was described in *Spalax* [75], then it was further demonstrated in the rat [89],

mouse [48], and Nile grass rat [61]. According to a study by Hattar *et al.*, [48] ipRGCs provide prominent retinal innervation of the mouse LHb.

If an expected reward has been instead of a unexpectedly negative outcome, neurons in the LHb will be activated, sending signals into the ventral tegmental area to inhibit dopaminergic neurons [90]. It has been suggested that the LHb is involved in the stress response and major depression [91, 92]. Moreover, deep brain stimulation of the LHb has been reported to be an effective therapy for severe treatment-resistant depression [93], suggesting that the LHb is a new potential target for the treatment of depression.

Dorsal Raphe Nucleus (DRN)

The DRN is the major area producing 5-HT for the forebrain, and is also one of the vital regions in response to light stimuli [55]. A retinal projection to the DRN has been found in many species, including cat [94], rat [95, 96], Mongolian gerbil [96, 97], tree shrew [98], *Octodon degus* [99], and the monkey *Cebus apella* [100]; but it is barely detectable in the mouse [48]. Light stimuli is able to significantly activate neuronal activity in the human brainstem through functional MRI detection [101], further based on the anatomical region of the human raphe [102], which suggests the existence of human retino-raphe circuitry. The 5-HT level in the human brain has been directly associated with the duration of sunlight and that can be increased rapidly with increased luminosity [103, 104]. The 5-HT output from the DRN has many functional activities, such as non-photon circadian entrainment of the pacemaker center in the SCN [105]. Although the retino-raphe projection modulates the 5-HT level [106], the action of this projection in light therapy has not yet been clearly elucidated.

Nevertheless, the DRN has frequently been highlighted in depression research [107], since the 5-HT system is thought to be an important neuronal circuit in depression [108, 109]. In fact, serotonergic axons from the raphe nucleus extensively innervate the cortex, hippocampus, Amy, BNST, and hypothalamus [110]. Depression seems to be more frequently associated with the DRN rather than the MRN, such as reduced neuron numbers and increased mRNA levels of tryptophan hydroxylase have been reported in the DRN of depressed patients [111, 112]. When using *Arvicanthis niloticus* (Nile grass rat) as a model of seasonal depression with light deprivation, it was found that a projection of orexin neurons from the perifornical-lateral hypothalamic area to the DRN is an

important pathway in light therapy [113]. However, the grass rat is thought to lack a direct retino-raphe projection [61]. That will differ from models with an obvious retino-raphe projection, since gerbils [114] and rats (unpublished data) both show a significant reduction of depression-like behavior by activation of the retino-raphe circuitry and by the bright light therapy; and this action is lost with specific elimination of the retino-raphe projections [114]. This finding suggests a novel neural circuit function with a retino-raphe projection underlying the effect of light therapy on depression.

In terms of retinofugal projections, the targets described above appear to be shared and have some common characteristics among various species [59, 60]. However, some targets only have sparse retinal fibers and there are some species differences, giving rise to small inconsistencies between different groups. For example, Johnson and collaborators reported that retinal projections to the BNST and Amy are absent in the rat [57]. However, the retino-raphe projection has been confirmed in the gerbil and rat by different groups [96, 115]. In addition, different regions receiving retinal projections are interconnected; for example, the 5-HT projection from the DRN strongly innervates the Amy, including its basolateral and medial areas [116–118], while the central Amy also sends afferent projections to both the dorsal and ventral DRN [119]. Thus the neural circuits can work together, contributing to the effect of light therapy on major depression.

Light Therapy Beyond Depression

Minor side-effects associated with light therapy mainly include dry eyes, sleep disturbance, and fatigue feeling; these are partly attributable to the light parameters used in therapy, such as dose (light intensity and duration of exposure), spectral content (enriched blue light or conventional white light), and method of exposure (including diffuse/focused, direct/indirect, and the angle of incidence relative to the eyes) [19]. The light parameters and conditions will be further optimized for better light therapy based on our understanding of the mechanism. However, the benefits of light therapy are likely to expand to other types of psychiatric disorders. Based on clinical case reports, these include attention deficit hyperactivity disorder [120], bipolar disorder [121], Parkinson's disease [122], and Alzheimer's disease [123]. Very recently, an animal study showed that the protein levels of Aβ associated with the symptoms in a mouse model of Alzheimer's

disease are significantly attenuated by LED light therapy with a gamma rhythm (40 Hz) [124]. This study implied that glial cells also take part in the effect of light therapy.

Summary and Implications

Accumulating evidence has demonstrated that light therapy is effective for seasonal and non-seasonal depression, as particularly demonstrated by double-blind, placebo-controlled, and randomized clinical trials nowadays [20, 21]. Compared with conventional treatment with antidepressant drugs like SSRI, light therapy has a relatively fast onset of therapeutic effect with minimal side-effects [19]; it might act through a unique pathway different from the chronic desensitization of pharmacological agents to 5-HT1a, 5-HT1b, and other receptors [125]. Nevertheless, it is clear that light therapy combined with psychopharmacological therapy seems to be a better option for some patients with major depression [6]. So far, the mechanism underlying the effect of light therapy is still unclear [5]. Among several emotional brain regions receiving retinal projections, the DRN with an evident retino-raphe projection appears to be a good candidate for being mainly responsible for light therapy. There is a direct retinal projection to the DRN in most rodents and primates [96, 100]. Moreover, 5-HT activity in the human brainstem occurs in response to light stimuli and is associated with depression [103, 104]. Our studies have shown that the retino-raphe projection in several species appears to be dominated by Y cells (also named alpha cells) [94, 115]. These cells with fast axonal conduction seem to match the relay condition of light signals into the 5-HT DRN system that primarily initiates the arousal response [25, 126]. Alteration of 5-HT production in the DRN is likely to underlie how light therapy exerts its therapeutic effect on depression and other mood disorders. On the other hand, current optogenetics studies have shown that light stimulation effectively modulates the activity of neurons that artificially express microbial opsins *via* viral transfection [127, 128]. And vertebrate opsins including rhodopsin [129], cone opsins [130], and melanopsin [131] could also be used as optogenetic tools to modulate neuronal activity. It was implicated that retinal cells with photoreceptors could affect neural circuitry function in brain, which might be a key basis for the effect of light therapy.

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