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光疗抗抑郁及其作用机制的研究进展*

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摘要 抑郁症是以显著而持久的情绪或心境低落为主要表现的精神疾病. 在各种治疗抑郁症的手段中，光疗因副作用小、成本低而受到越来越多的关注. 光疗作为一种物理治疗方法，利用人工光源或自然光源，通过不同时长和不同强度的光线照射达到防治疾病和辅助治疗的目的. 动物实验和临床试验均验证了光疗能有效缓解抑郁症状. 然而，目前光疗抗抑郁作用的神经机制还未完全明确，光疗的应用范式也尚存争议. 本文简述了光疗在抑郁症中的临床应用及光疗抗抑郁的神经机制，为光疗抗抑郁的优化及推广提供理论支持.

关键词 抑郁症，光疗，内在光敏感视神经节细胞，情绪障碍
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根据美国精神病学会第五版《精神疾病诊断和统计手册》（The Diagnostic and Statistical Manual of Mental Disorders，DSM），抑郁障碍包括重性抑郁障碍（重性抑郁发作）、破坏性心境失调障碍、持续性抑郁障碍（恶劣心境）、经期前烦躁障碍、物质/药物所致的抑郁障碍、其他躯体疾病所致的抑郁障碍以及其他特定和非特定的抑郁障碍. 这些抑郁障碍的共同特点是存在悲伤、空虚或易激惹心境，并伴随躯体和认知改变，显著影响个体功能[1]. 不同抑郁障碍之间的差异包括病程、时间及病因等. 此外，DSM-IV将双相及相关抑郁障碍归于抑郁障碍的范畴. 一些研究者将严重程度未达到抑郁症诊断标准但有抑郁表现的一种情感障碍定义为阈下抑郁症（subthreshold depression，SD）[2].

目前抑郁症发病机制并不完全清楚，主流的假说有：a. 单胺类神经递质假说；b. 下丘脑-垂体-肾上腺（hypothalamic-pituitary-adrenal，HPA）轴功能亢进假说；c. 炎症因子和神经营养因子（neurotrophic factors，NTF）假说等. 抑郁症可能是由于单胺类神经递质及其受体、HPA轴功能失调、NTF和炎症反应等多种原因共同作用和相互影响的结果.

目前，药物是抑郁症的主要治疗手段，但抗抑郁药物治疗普遍存在起效慢、疗程长及复发率高等局限性，并且长期使用可能产生诸多副作用，例如性功能障碍、体重增加、恶心和头痛等[3]. 另外，约1/3的重度抑郁症（major depressive disorder，MDD）患者对现有的抗抑郁药物应答不理想[4]. 因此，如何快速抗抑郁以及提高当前抑郁症的缓解率是人们研究的重点之一.

光疗（light therapy，LT）是通过不同时长和不同强度的光线照射防治疾病的一种物理治疗方法，具有副作用小、成本低、安全性高等优势. 动物实验[5]和临床试验[6]均已证明，光疗能有效缓解抑郁症状并减少残留症状，在抑郁症的治疗中有很好的应用前景. 然而，其确切的抗抑郁机制尚不明确. 本文介绍了光疗在抑郁症中的临床应用现状及其作用机制，为光疗抗抑郁的优化和推广提供理论支持.

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1 光疗抗抑郁的临床应用现状

光疗最初被用于治疗季节性抑郁症（seasonal depressive disorder，SDD），随后临床研究发现，光疗对双相情感障碍（bipolar disorder，BD）的抑郁相[7]、SD和围产期抑郁症（perinatal depression，PPD）等非季节性抑郁症的治疗也有一定效果.

1.1 光疗有效干预SDD

SDD是因冬季短暂的光照引起的一种周期性情感障碍，常在秋冬出现，春夏缓解. 主要症状包括注意力不集中、情绪低落、社交减退等. 症状常在特定季节出现，并且持续两年以上[8]. 大量随机双盲对照实验已经证明，光疗是SDD的一种有效的干预手段[9]，并且在治疗指南中，光疗已经作为SDD的一线疗法用于临床[10]. 此外，SDD患病人群多在北纬30°以北或者南纬30°以南，预防性光疗使SDD的发病风险降低了36%[11].

冬季光周期缩短是SDD的重要危险因素之一. 光照参与5-羟色胺（5-hydroxytryptamine，5-HT）、褪黑素（melatonin，MT）以及昼夜节律的调节. 光照不足降低5-HT合成依赖的维生素D水平，进而导致5-HT合成减少. 秋冬季较短的光照增强与5-HT再摄取有关的5-HT转运蛋白的结合力，进一步降低突触间隙5-HT浓度. 光疗可通过降低前扣带皮层（anterior cingulate cortex，ACC）和前额叶（prefrontal cortex，PFC）的5-HT转运蛋白含量，从而减少突触间隙5-HT的再摄取[12]. Spies等[13]的研究中发现，健康对照者的单胺氧化酶（monoamine oxidase，MAO）水平在秋冬到春夏呈下降趋势，而SDD患者变化并不明显，提示SDD患者单胺氧化酶水平的季节性动态调节受损，而在3周的光疗后，SDD患者的单胺氧化酶水平降低，进而增加5-HT水平缓解抑郁. 突触间隙5-HT浓度降低是抑郁症发病机制的经典假说之一. 此外，光照减少会升高SDD患者的MT水平，正常情况下MT在夜晚增加有助于睡眠，但持续增加将会导致昼夜节律紊乱、精力减退等症状. 视网膜电图（electroretinogram）发现，SDD患者在冬季普遍出现视网膜光敏性降低，光疗干预后或者在夏季其视网膜光敏性恢复正常[14]. 此外，多巴胺生物合成的限速酶——酪氨酸羟化酶（tyrosine hydroxylase，TH），其基因表达依赖于光周期，在冬季TH基因表达明显下调[14]. 综上所述，光疗可以调节SDD患者因光照不足而导致的激素和神经递质水平紊乱，从而发挥抗抑郁作用. 有研究表明，SDD患者在冬季表现出更高的巨噬细胞活性和更低的淋巴细胞增殖，且在4周光疗后，巨噬细胞活性降低以及淋巴细胞增殖增加，这一结果支持SDD的炎症假说并且证实光疗的免疫调节作用[15].

1.2 光疗辅助BD治疗

BD是一种以抑郁、躁狂反复发作为主要症状的慢性精神疾病[16]. 由于在BD治疗过程中，抑郁状态极易转换为躁狂状态，因此临床上常用心境稳定剂和非典型抗精神病药，而不建议单独使用抗抑郁药[17]. 据报道，光疗是BD的有效辅助治疗[18]，且光疗诱导的转躁狂风险（2.3%）远低于抗抑郁药（15%~40%）[19].

日常暴露于强光中可以有效缓解BD患者的抑郁症状[20]，同时有报道称，虚拟黑暗环境下可以在一定程度上缓解BD患者的躁狂状态[21]. Hirakawa等[18]提出“光调节”疗法，即抑郁状态的光疗和躁狂状态的黑暗疗法相结合，动态调整BD患者的情绪. 此外，有报道称，早上接受阳光直射的BD患者病情恢复得较快[22]，继而提出黎明模拟光疗，即在早晨1.0~2.5 h内将曝光量从0 lux增加到200~300 lux[23]. 荟萃分析研究显示，黎明模拟光疗对季节性和非季节性抑郁症均有显著的抗抑郁和降低复发率的作用[24-25]. 对于BD的复发性和难治性，光疗作为一种非药理学抗抑郁手段，是一种快速、有效、安全的临床干预方式[26].

1.3 光疗在SD中的临床应用现状

SD是指严重程度未达到抑郁症诊断标准但有抑郁表现的一种精神疾病. 患病人群以青少年居多，据报道，中国32%的大学生[2]患有SD. SD患者生活质量下降，自杀风险增加，发展为MDD的风险为10%~25%，已经构成了高危人群. 但考虑到抗抑郁药的高风险低效益，美国国家卫生研究院治疗指南提出不应常规使用抗抑郁药治疗阈下和轻度抑郁症. 目前，主要用心理干预缓解SD的相关症状. 但心理干预存在起效慢、疗效低、成本高及依从性差等缺点. 一项针对142名SD学生的随机双盲对照实验发现，高强度（LT-5 000；效应量 d = 1.56，95% CI：1.15~1.98）和低强度（LT-500；效应量 d = 0.84，95% CI：0.43~1.26）的光疗对于治疗SD患者均是有效的，且LT-5 000干预结果更为明显[27]. 这提示光疗在阈下及轻度抑郁症中有很好的应用前景，但也需要更多的临床试验进一步验证.

1.4　光疗与药物联合使用治疗MDD

MDD患者病情严重复杂，有极高的发病率、复发率及自杀风险，因此治疗难度也更大. 有研究提出，光疗和氟西汀联合使用抗抑郁效果更为显著. Lam等[28]对122名MDD患者进行了一项为期8周的随机双盲对照实验，结果表明光疗（效应量d = 0.80，95% CI：0.28~1.31）以及光疗与氟西汀联合使用（效应量d = 1.11，95% CI：0.54~1.64）在蒙哥马利-艾森贝格抑郁评定量表（Montgomery-Asberg depression rating scale，MADRS）评分变化方面显著优于安慰剂，均可缓解抑郁症状，且联合使用效果更好（P = 0.02）. 这与Güzel Özdemir等[29]的结果一致，他们比较了文拉法辛单独使用以及联合光疗的效果，两组汉密尔顿抑郁量表（Hamilton depression rating scale，HDRS）抑郁评分在第1周均有所下降，且光疗联合文拉法辛治疗组评分下降更快、缓解率也更高. 在干预时间为5周的397名MDD患者中，光疗和药物的组合明显优于药物和安慰剂组合（standardized mean difference，SMD，SMD = 0.56［0.24~0.88］；P < 0.001）治疗[30]. 光疗似乎增强了抗抑郁药物的作用，甚至在药物治疗开始时进行1周的光疗也能加速治疗反应，缩短药物缓解抑郁所需的时间. 此外，Prasko等[31]的研究结果发现，强光单独暴露以及强光疗法联合丙咪嗪均可有效治疗非季节性重性抑郁症. 这些临床研究结果为光疗在MDD患者中的应用提供了理论依据. 目前有多项研究支持单一光疗[23，32]或联合药物[33]在MDD中的安全性、耐受性和有效性，且光疗联合抗抑郁药物效果比单一药物治疗更好，然而目前并不清楚光疗增强抗抑郁药物的作用机制.

1.5　光疗在特殊人群抑郁症中的临床应用前景

光疗可以用于抗抑郁药物禁忌症患者，例如有其他合并症的老年抑郁患者、孕妇和哺乳期妇女等. PPD是一种影响妇女孕期和产后1年的严重抑郁情绪障碍. 孕妇在怀孕期间由于激素水平的紊乱，情绪起伏较大，抑郁风险较高，尽管DSM-V中没有单独提出PPD的诊断，但据统计约5%~10%孕妇患有抑郁症[34]. 在北美地区，5%~13%的孕妇服用抗抑郁药[35]；在荷兰，2%~3%的孕妇使用抗抑郁药[36]. 然而，抗抑郁药在孕期的安全性是有争议的[37]. 由于光疗的安全性高、起效快，孕妇可以及时接受治疗，避免病情进一步恶化并且婴儿也将从这种治疗中受益，光疗有望成为PPD中一种很好的替代治疗手段. 在患有非季节性抑郁症孕妇中进行的两项小型（n=10和n=27）随机对照试验表明，与安慰剂相比，光疗干预的患者抑郁症状显著缓解，且光疗效果与抗抑郁药物的效果相当[38-39]. 然而，也有临床试验（n=67）结果显示，光疗组（9 000 lux，5 000 K；缓解率40.6% ~ 53.1%）和安慰剂组（100 lux，5 000 K；缓解率50.9%~66.7%）HDRS抑郁评分都有所下降，但没有统计学差异[40]. 因此，有必要通过大样本、多中心的研究确定光疗在PPD患者中的有效性. 卒中后抑郁（post stroke depression，PSD）是卒中幸存者常见的精神症状之一[41]，在DSM-V中归于其他疾病导致的抑郁症. PSD主要表现为抑郁、兴趣减退、智力障碍和睡眠障碍. 研究表明，与单一使用艾斯西酞普兰治疗相比，联合强光治疗可提高睡眠质量（P = 0.020）并改善抑郁症状（P < 0.001）[42].

2　光疗抗抑郁的作用机制研究

光疗可以有效改善情绪和认知功能，这可能与光疗影响多个脑区的活动、功能连接和可塑性有关（图1）. 光疗通过视网膜将光信号转为电信号进而传输到中枢神经系统发挥作用. 视网膜神经系统中视杆和视锥细胞作为感光细胞主要参与视觉成像系统，此外，表达视黑蛋白的内在光敏感视神经节细胞（intrinsically photosensitive ganglion cells，ipRGC）[43]作为第三种感光细胞，在视觉非成像系统中发挥重要作用[44]. 视觉非成像系统是指光信号通过ipRGC投射到高级脑区参与昼夜节律、情绪、认知等功能的调节. 其中外侧膝状体（lateral geniculate nuclei，LGN）被认为是视觉信息通路的中继站，上丘（superior colliculus，SC）负责视觉运动信息处理，下丘脑（hypothalamus）参与激素调节[45-46]. 视觉投射的诸多核团与情绪调节密切相关，尤其是杏仁核（amygdaloid nucleus）、外侧僵核（lateral habenula，LHB）、视交叉上核（suprachiasmatic nucleus，SCN）和中缝背核（dorsal raphe nucleus，DRN）等. 视觉信息通路与这些核团的环路被认为是光疗发挥抗抑郁作用的主要机制.

2.1　光疗通过光敏神经环路缓解抑郁

LHB是介导前脑、中脑、后脑的单胺能系统

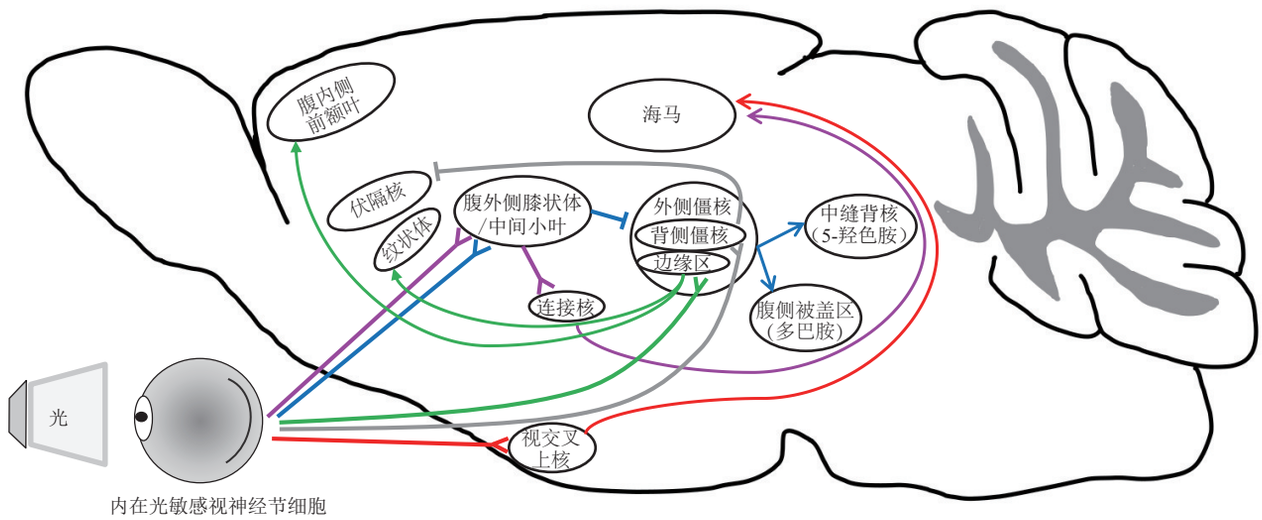

Fig. 1　Light affects mood and learning through distinct retina−brain pathways

图1　光通过不同的神经环路影响情绪和认知

光激活内在光敏感视神经节细胞-激活腹外侧膝状体/中间小叶（GABA能神经元）- 抑制外侧僵核（CaMKIIα神经元）- 中缝背核（5-羟色胺）、腹侧被盖区（多巴胺）缓解抑郁[47]（蓝色实线）；内在光敏感视神经节细胞-激活外侧僵核边缘区-腹内侧前额叶、纹状体参与光对情绪的调节[48]（绿色实线）；内在光敏神经节细胞-激活腹外侧膝状体/中间小叶-激活连接核在光疗改善空间记忆中发挥作用（紫色实线）[49]，内在光敏感视神经节细胞-激活视交叉上核-海马参与光对认知的调节[48]（红色实线）. 此外，夜间光照激活内在光敏感视神经节细胞-激活背侧僵核-抑制伏隔核，诱发小鼠抑郁情绪[50]（灰色实线）.

通信的一个关键核团，涉及抑郁、焦虑、疼痛、奖赏决策等功能. 先前研究表明，LHB放电异常升高与情绪低落[51]和快感缺乏等抑郁症状紧密相关[52]. 并且，异常升高的LHB放电可以被抗抑郁药物显著逆转[53]，LHB功能异常被认为是抑郁症发病机制之一. Huang等[47]发现，ipRGC-LGN-LHB是光疗抗抑郁的神经通路之一. 光疗通过激活ipRGC支配的腹外侧膝状体（ventral lateral geniculate nucleus，vLGN）和中间小叶（intergeniculate leaflet，IGL）的GABA能神经元，抑制LHB的异常放电，从而缓解小鼠的抑郁样行为. LHB向腹侧被盖区（ventral tegmental area，VTA）和DRN发出投射，VTA和DRN分别是前脑产生DA和5-HT的主要区域，也是响应光刺激的重要区域脑区之一. 抑郁症患者DRN中神经元数量减少，色氨酸羟化酶mRNA水平增加[54]. 提示光疗可能通过影响脑区的活动来调节神经递质的释放，进而发挥抗抑郁作用.

此外，有文献报道ipRGC-外侧僵核边缘区（perihabenular region，PHb）环路也参与了情绪调节. PHb与LHB相邻，是光调节情绪的基础. PHb接受ipGRC的直接输入，并向mPFC、背侧和腹侧纹状体（striatum）等与情感相关的脑区发出投射. 在不规则的光周期下，PHb神经元活动增加且伴随着抑郁、烦躁等消极情绪的改变，而失活PHb神经元可以阻止异常光循环诱发的情绪变化[48].

2.2　光疗通过调节单胺能神经递质改善抑郁

单胺能神经递质的功能活性降低被认为是抑郁症发病的重要机制之一. 光疗可能参与单胺能神经递质的合成、释放、再摄取、降解过程. 四氢生物蝶呤（tetrahydrobiopterin）是色氨酸羟基化和5-HT合成中必不可少的辅因子，其水平降低可增加抑郁发作的易感性. Hoekstra等[55]对19例SDD患者与对照组进行光疗前后血浆生物蝶呤水平的测定，发现SDD患者四氢生物蝶呤水平较低，而光疗后四氢生物蝶呤的水平增加. Lambert等[56]采集101名健康男性颈内静脉血液标本，评估5-HT代谢物浓度和季节及光照的关系，证实大脑5-HT释放速度与光的持续时间和光照强度成正相关. SDD患者抑郁期间5-HT转运体功能亢进，光疗可降低5-HT转运体功能，减少5-HT的再摄取进而提高突触间隙5-HT水平[57]. 光疗还可以增强大部分脑区的多巴胺能传输[58]. 日间活动的啮齿类动物在模拟冬季光周期下前脑多巴胺含量改变，出现节律行为改

变，且在接受光照后恢复，表明光疗通过多巴胺能回路对节律行为产生影响[59]. 关于光疗对去甲肾上腺素的影响目前没有相关报道. 以上研究提示，光疗通过干预神经递质合成、再摄取等途径发挥抗抑郁作用.

2.3　光疗对激素的影响可能是改善抑郁机制之一

光疗可通过HPA轴参与生物钟的调节. 皮质醇（cortisol）分泌受HPA轴的调控，在抗压中扮演重要角色，又被称为“压力荷尔蒙”. HPA轴活动由下丘脑室旁核（paraventricular nucleus of hypothalamus，PVN）中的小细胞神经分泌细胞分泌的促肾上腺皮质激素释放因子（corticotropin-releasing factor，CRF）调控，该因子激活垂体前叶促肾上腺皮质激素（adrenocorticotrophic hormone，ACTH）的分泌，进而刺激肾上腺皮质中皮质醇的产生和释放. 抑郁症患者下丘脑PVN的CRF神经元过度活跃皮质醇水平常有升高[60]. CRF和ACTH的抑制由皮质醇通过糖皮质激素受体（glucocorticoid receptor，GR）介导. GR功能受损导致HPA轴的过度活跃即皮质醇的抑制减少是抑郁症的发病假说之一. 啮齿类动物研究表明，在小鼠出生后光照环境的改变会对HPA轴和昼夜节律系统产生长期影响，从而导致成年后应激反应的改变和抑郁表型[61]. 以上提示光对HPA轴有影响，但是具体机制还需要大量的深入研究. 另外，可以确定的是，光照强度和皮质醇水平密切相关[60]. 光可以通过SCN交感神经系统诱导肾上腺基因表达，这种基因表达增加伴随着血浆和大脑皮质醇水平的升高. 但关于光疗对皮质醇水平的影响说法不一，有研究表明光疗会使人血液皮质醇水平升高[62]，也有研究指出光疗可以降低皮质醇水平[63]，因此还需要大量的研究证实光疗对激素水平的确切影响.

光疗能抑制MT的分泌，这被认为是其抗抑郁作用机制之一. MT是一种调节昼夜节律和促进睡眠的激素，由松果体（pined body）产生和分泌，其节律由SCN控制. SCN与松果体相互作用，白天光刺激SCN后将信号传送到松果体，抑制MT的分泌，降低血液中MT浓度，从而减轻困倦. 相反，在夜间没有光照的情况下，SCN不再抑制松果体，MT血液浓度升高并在清晨达到峰值，然后缓慢降低，促进觉醒. 光疗可以通过激活ipRGCs进而抑制松果体，减少MT在白天的合成和释放，使生物钟恢复稳态[64].

2.4　光生物调节发挥抗抑郁的潜在机制

光生物调节（photobiomodulation，PBM）基于非视网膜暴露的红外（infrared，IR）和近红外（near-infrared，NIR）发挥作用，主要参与降低炎症、氧化应激水平、促进代谢、调节细胞凋亡等[65]. 研究表明，经颅NIR（800 nm）可减少创伤性脑损伤（traumatic brain injury，TBI）小鼠模型的神经炎症[66]. 此外，束缚应激的抑郁模型中，PBM干预可以减轻小鼠的抑郁行为，抑制海马和前额叶中的神经炎症反应，同时细胞凋亡标志物也有下调[67]. 抑郁症患者炎症因子增加[68]，且炎症因子的增加与抑郁症的难治性密切相关[69]. 但是PBM是否可以通过抗炎作用缓解抑郁尚未明确，针对MDD的PBM研究仍处于初步阶段. 抑郁症与大脑代谢减退和线粒体功能障碍有关. PBM干预为细胞色素c氧化酶（cytochrome c oxidase，CCO）提供能量并刺激线粒体呼吸链，增加ATP产生，增强线粒体活性. 此外，PBM还可以通过促进一氧化氮（nitric oxide，NO）从CCO解离，释放氧的结合位点并恢复氧化磷酸化来提高线粒体活性. PBM可能对MAO和氧化应激产生有益影响. MAO催化单胺类物质氧化脱氨反应诱导单胺类递质的降解. 有报道称，抑郁症患者MAO常有升高[70]，且MAO抑制剂可有效缓解抑郁. 在抑郁模型鼠中每天使用低强度NIR经颅照射2周后发现MAO活性降低，并减少了由MAO催化的单胺氧化脱氨反应过程中活性氧（reactive oxygen，ROS）的产生[71]. 此外，NIR可以诱导ROS的短时间爆发，导致抗氧化机制的激活[72]. 这些发现为PBM抗抑郁和抗氧化作用提供了证据.

2.5　视网膜–VLGN/IGL–连接核通路参与光疗改善空间记忆

研究发现，视网膜和连接核（nucleus reuniens，RE）的双突触视觉回路介导光改善认知功能的神经机制. RE位于丘脑中线部位，是前额叶投射到海马的重要中继站，通过RE来改善皮质信息流对于调节情绪以及建立类似抑郁的病理状态至关重要. RE的损伤或失活会降低前额叶-海马回路的连贯性，诱发小鼠的类抑郁样行为[73]. 光通过在视网膜中表达SMI-32的ON型视网膜神经节细胞激活vLGN和IGL中的CaMKIIα神经元，进而激活RE中的CaMKIIα神经元，发挥增强记忆的作用. 而抑制RE神经元会显著降低光疗对空间记忆的改善作用. 由此证明了ipRGC-vLGN/IGL-RE通

路的激活是光疗增强空间记忆的基础[49]. SCN除了调节昼夜节律，对认知也有一定影响[48]. 敲除ipRGC发育的转录因子Brn3b，使ipRGC仅保留投射到SCN的通路，发现在异常光周期（3.5 h黑夜/3.5 h白天）且不改变SCN昼夜节律的情况下，小鼠的认知受损. 这可能是光疗发挥作用的另一种潜在机制.

3 光疗的注意事项

目前，国内外对于光疗的应用范式并没有统一的标准（表1）. 光照时机、持续时间、光照强度、光源、光疗设备等没有标准化，临床应用需根据患者的症状制定个体化光疗方案. 根据光疗照射时间段可分为晨光疗法、午间疗法、晚间疗法和全天疗法. 晨光疗法对昼夜节律影响较大，有研究表明，虽然BD患者对晨光疗法的敏感性较高，但晨光疗法会增加患者转躁狂的风险[74]，因此建议对BD患者先给予午间光疗15 min[75]. 光疗时间太长可能会产生与视觉有关的副作用，时间太短则效果不佳，目前研究表明30~60 min效果较好[76]. 此外，无论是自然光还是手机或电脑等电子设备，夜间光暴露均与抑郁症患病率相关[77]. 夜间和白天光暴露分别导致类抑郁[50]和抗抑郁[47]，表明光对情绪或认知的影响与昼夜节律有关. An等[50]发现，夜间光暴露致类抑郁由ipRGCs-dpHb-NAc通路介导. 投射到NAc的dpHb神经元受昼夜节律调节，在夜间更容易激活，并优先响应夜间光信号的输入[50]，dpHb接受ipRGCs输入，进而抑制NAc的活动从而诱导抑郁情绪. 这为光疗在不同昼夜节律阶段对情绪产生不同的结果提供了理论依据. 与光疗有关的副作用主要包括眼睛干燥、视力模糊、睡眠障碍和疲劳感等. 对高血压模型大鼠应用光疗后大鼠血压升高，表明光疗有加重高血压的风险[78]. 在患者进行光疗时，如出现不适感应及时调整光参数，如光强度、曝光时间、光谱含量（蓝光或常规白光）以及曝光方法（扩散/聚焦、直接/间接、相对于眼睛的入射角度）等.

Table 1 Summary of phototherapy paradigm

表1 光疗范式总结

抑郁类型	时间段	时长/min	周期[1)]	光照强度/lux	参与人数	评分量表	缓解率/%	参考文献
SDD	4:30~6:00	90	6 w	250	95	HDRS	60.0	[79]
	19:00前	30~60	6 w	10 000	57	HDRS	74.0	[80]
	7:00~8:00	30	8 w	10 000	96	HDRS	50.0	[9]
	醒后10 min	30	3 w	10 000	94	HDRS	57.1	[81]
	7:30~11:00	30	12 d	10 000	73	HDRS	50.0	[82]
BD	6:00	30	4 w	400	9	HDRS	50.0	[83]
	早上	120	3 d	5 000	49	HDRS	63.2	[84]
	12:00~14:00	45-60	8 w	7 000	9	HDRS	50.0	[75]
	醒后	7.5~45	8 w	7 000	44	HDRS	50.0	[85]
	8:00~9:00	30	2 w	10 000	50	HDRS	28.8	[86]
	6:30~9:00	60	2 w	5 000	74	HDRS	78.2	[87]
	12:00~14:30	15~60	6 w	7 000	45	HDRS	68.2	[88]
SD	12:00前	30	8 w	5 000	142	HDRS	76.0	[27]
MDD	6:00~9:00	30	1 w	10 000	13	HDRS	27.0	[89]
	醒后10:00前	60	5 w	10 000	102	HDRS	41.7	[90]
	早上	60	3 w	7 500	89	HDRS	54.0	[91]
	7:00	60	8 w	7 000	50	HDRS	76.0	[29]
	7:00~8:00	30	8 w	10 000	60	MADRS	43.8	[28]
PPD	醒后10 min	60	5 w	7 000	27	HDRS	81.3	[39]
	醒后30 min	30	6 w	9 000	67	HDRS	53.1	[40]
PSD	8:00~9:00	30	6 w	10 000	112	HDRS	71.4	[42]

[1)]w, 周.

4　总结与展望

通过动物实验和随机双盲对照临床试验的研究，越来越多的证据表明光疗能有效缓解抑郁. 与使用抗抑郁药常规治疗相比，光疗具有起效快、副作用小的优势，是一种值得推广的抗抑郁手段. 目前认为，光通过视觉非成像系统干预情绪和认知，表明光疗的治疗效果依赖于特定神经通路的完整性，且需要长时间坚持接受光疗干预，才能使相应神经通路发生生理性改变. 但是目前并不清楚，对于光疗依赖的特定神经通路损伤的抑郁患者，光疗是否仍然有效. 另外，光疗对SDD、BD的抑郁相、MDD以及SD等有缓解抑郁的作用. 然而，光疗对不同类型的抑郁患者的抗抑郁效果是否存在共性或者显著性差别，光疗对抑郁伴随的认知损伤是否有改善作用均未见相关报道. 当前对于光疗抗抑郁的神经机制研究有限，光疗抗抑郁作用机制还未完全明确，光疗抗抑郁的生理生化机制还有待探索. 进一步大样本、多中心的临床队列研究和动物实验有望给出光疗抗抑郁的实用效果，并为光疗以应用范式行业标准化提供理论和试验基础.

参　考　文　献

[1] Dillon D, Pizzagalli D. Mechanisms of memory disruption in depression. Trends Neurosci, 2018, **41**(3): 137-149

[2] Jiang L, Wang Y, Zhang Y, *et al*. The reliability and validity of the center for epidemiologic studies depression scale (CES-D) for Chinese university students. Front Psychiatry, 2019, **10**:315

[3] Moret C, Isaac M, Briley M. Problems associated with long-term treatment with selective serotonin reuptake inhibitors. J Psychopharmacol, 2009, **23**(8): 967-974

[4] Daly E, Singh J, Fedgchin M, *et al*. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA psychiatry, 2018, **75**(2): 139-148

[5] Chen S, Badea T, Hattar S. Photoentrainment and pupillary light reflex are mediated by distinct populations of ipRGCs. Nature, 2011, **476**(7358): 92-95

[6] Vandewalle G, Schwartz S, Grandjean D, *et al*. Spectral quality of light modulates emotional brain responses in humans. Proc Natl Acad Sci USA, 2010, **107**(45): 19549-19554

[7] Hirakawa H, Terao T, Muronaga M, *et al*. Adjunctive bright light therapy for treating bipolar depression: a systematic review and meta-analysis of randomized controlled trials. Brain Behav, 2020, **10**(12): e01876

[8] Nussbaumer-Streit B, Thaler K, Chapman A, *et al*. Second-generation antidepressants for treatment of seasonal affective disorder. Cochrane Database Syst Rev, 2021, **3**(3):CD008591

[9] Lam R, Levitt A, Levitan R, *et al*. The Can-SAD study: a randomized controlled trial of the effectiveness of light therapy and fluoxetine in patients with winter seasonal affective disorder. Am J Psychiatry, 2006, **163**(5): 805-812

[10] Pail G, Huf W, Pjrek E, *et al*. Bright-light therapy in the treatment of mood disorders. Neuropsychobiology, 2011, **64**(3): 152-162

[11] May I. Light therapy for preventing seasonal affective disorder: summary of a Cochrane review. Explore (NY), 2020, **16**(2): 133-134

[12] Harrison S, Tyrer A, Levitan R, *et al*. Light therapy and serotonin transporter binding in the anterior cingulate and prefrontal cortex. Acta Psychiatr Scand, 2015, **132**(5): 379-388

[13] Spies M, James G, Vraka C, *et al*. Brain monoamine oxidase A in seasonal affective disorder and treatment with bright light therapy. Transl Psychiatry, 2018, **8**(1): 198

[14] Okimura K, Nakane Y, Nishiwaki-Ohkawa T, *et al*. Photoperiodic regulation of dopamine signaling regulates seasonal changes in retinal photosensitivity in mice. Sci Rep, 2021, **11**(1): 1843

[15] Song C, Luchtman D, Kang Z, *et al*. Enhanced inflammatory and T-helper-1 type responses but suppressed lymphocyte proliferation in patients with seasonal affective disorder and treated by light therapy. J Affect Disord, 2015, **185**:90-96

[16] Saccaro L, Schilliger Z, Dayer A, *et al*. Inflammation, anxiety, and stress in bipolar disorder and borderline personality disorder: a narrative review. Neurosci Biobehav Rev, 2021, **127**:184-192

[17] Malhi G, Outhred T, Morris G, *et al*. Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders: bipolar disorder summary. Med J Aust, 2018, **208**(5): 219-225

[18] Hirakawa H, Terao T, Shirahama M. Light modulation for bipolar disorder: a commentary on "an update on adjunctive treatment options for bipolar disorder" by Dean *et al*. (2018). Bipolar Disord, 2019, **21**(3): 282

[19] Benedetti F. Rate of switch from bipolar depression into mania after morning light therapy: a historical review. Psychiatry Res, 2018, **261**:351-356

[20] Esaki Y, Kitajima T, Obayashi K, *et al*. Daytime light exposure in daily life and depressive symptoms in bipolar disorder: a cross-sectional analysis in the APPLE cohort. J Psychiatr Res, 2019, **116**: 151-156

[21] Henriksen T, Skrede S, Fasmer O, *et al*. Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial. Bipolar Disord, 2016, **18**(3): 221-232

[22] Benedetti F, Colombo C, Barbini B, *et al*. Morning sunlight reduces length of hospitalization in bipolar depression. J Affect Disord, 2001, **62**(3): 221-223

[23] Golden R, Gaynes B, Ekstrom R, *et al*. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry, 2005, **162**(4): 656-662

[24] Geoffroy P, Bellivier F, Scott J, *et al*. Seasonality and bipolar disorder: a systematic review, from admission rates to seasonality of symptoms. J Affect Disord, 2014, **168**:210-223

[25] Esaki Y, Obayashi K, Saeki K, *et al*. Preventive effect of morning light exposure on relapse into depressive episode in bipolar disorder. Acta Psychiatr Scand, 2021, **143**(4): 328-338

[26] Dallaspezia S, Benedetti F. Antidepressant light therapy for

bipolar patients: a meta-analyses. J Affect Disord, 2020, **274**: 943-948

[27] Jiang L, Zhang S, Wang Y, *et al*. Efficacy of light therapy for a college student sample with non-seasonal subthreshold depression: an RCT study. J Affect Disord, 2020, **277**: 443-449

[28] Lam R, Levitt A, Levitan R, *et al*. Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. JAMA Psychiatry, 2016, **73**(1): 56-63

[29] Güzel Özdemir P, Boysan M, Smolensky M, *et al*. Comparison of venlafaxine alone versus venlafaxine plus bright light therapy combination for severe major depressive disorder. J Clin Psychiatry, 2015, **76**(5): e645-654

[30] Geoffroy P, Schroder C, Reynaud E, *et al*. Efficacy of light therapy versus antidepressant drugs, and of the combination versus monotherapy, in major depressive episodes: a systematic review and meta-analysis. Sleep Med Rev, 2019, **48**: 101213

[31] Prasko J, Horacek J, Klaschka J, *et al*. Bright light therapy and/or imipramine for inpatients with recurrent non-seasonal depression. Neuro Endocrinol Lett, 2002, **23**(2): 109-113

[32] Al-Karawi D, Jubair L. Bright light therapy for nonseasonal depression: meta-analysis of clinical trials. J Affect Disord, 2016, **198**:64-71

[33] Morton E, Michalak E, Levitt A, *et al*. Quality of life impacts of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. Can J Psychiatry, 2021, **66**(3): 289-297

[34] Gavin N, Gaynes B, Lohr K, *et al*. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol, 2005, **106**: 1071-1083

[35] Daw J, Mintzes B, Law M, *et al*. Prescription drug use in pregnancy: a retrospective, population-based study in British Columbia, Canada (2001-2006). Clin Ther, 2012, **34**(1): 239-249.e2

[36] Jimenez-Solem E, Andersen J, Petersen M, *et al*. Prevalence of antidepressant use during pregnancy in Denmark, a nation-wide cohort study. PLoS One, 2013, **8**(4): e63034

[37] Tuccori M, Testi A, Antonioli L, *et al*. Safety concerns associated with the use of serotonin reuptake inhibitors and other serotonergic/noradrenergic antidepressants during pregnancy: a review. Clin Ther, 2009, **Pt 1**: 1426-1453

[38] Epperson C, Terman M, Terman J, *et al*. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry, 2004, **65**(3): 421-425

[39] Wirz-Justice A, Bader A, Frisch U, *et al*. A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. J Clin Psychiatry, 2011, **72**(7): 986-993

[40] Bais B, Kamperman A, Bijma H, *et al*. Effects of bright light therapy for depression during pregnancy: a randomised, double-blind controlled trial. BMJ Open, 2020, **10**(10): e038030

[41] Towfighi A, Ovbiagele B, El Husseini N, *et al*. Poststroke depression: a scientific statement for healthcare professionals from the American heart association/American stroke association. Stroke, 2017, **48**(2): e30-e43

[42] Xiao M, Feng L, Wang Q, *et al*. The therapeutic effects and safety of bright light therapy combined with escitalopram oxalate on insomnia in patients with poststroke depression. Int J Geriatr Psychiatry, 2021, **36**(1): 182-189

[43] Mure L. Intrinsically photosensitive retinal ganglion cells of the human retina. Front Neurol, 2021, **12**:636330

[44] Berson D, Dunn F, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science, 2002, **295**(5557): 1070-1073

[45] Hattar S, Kumar M, Park A, *et al*. Central projections of melanopsin-expressing retinal ganglion cells in the mouse. J Comp Neurol, 2006, **497**(3): 326-349

[46] Pickard G, Sollars P. Intrinsically photosensitive retinal ganglion cells. Rev Physiol Biochem Pharmacol, 2012, **162**: 59-90

[47] Huang L, Xi Y, Peng Y, *et al*. A visual circuit related to habenula underlies the antidepressive effects of light therapy. Neuron, 2019, **102**(1): 128-142.e128

[48] Fernandez D, Fogerson P, Ospri L L, *et al*. Light affects mood and learning through distinct retina-brain pathways. Cell, 2018, **175**(1): 71-84.e18

[49] Huang X, Huang P, Huang L, *et al*. A visual circuit related to the nucleus reuniens for the spatial-memory-promoting effects of light treatment. Neuron, 2021, **109**(2): 347-362.e7

[50] An K, Zhao H, Miao Y, *et al*. A circadian rhythm-gated subcortical pathway for nighttime-light-induced depressive-like behaviors in mice. Nat Neurosci, 2020, **23**(7): 869-880

[51] Yang L, Hu B, Xia Y, *et al*. Lateral habenula lesions improve the behavioral response in depressed rats *via* increasing the serotonin level in dorsal raphe nucleus. Behav Brain Res, 2008, **188**(1): 84-90

[52] Li K, Zhou T, Liao L, *et al*. βCaMKII in lateral habenula mediates core symptoms of depression. Science, 2013, **341**(6149): 1016-1020

[53] Li B, Piriz J, Mirrione M, *et al*. Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. Nature, 2011, **470**(7335): 535-539

[54] Boldrini M, Underwood M, Mann J, *et al*. More tryptophan hydroxylase in the brainstem dorsal raphe nucleus in depressed suicides. Brain Res, 2005, **1041**(1): 19-28

[55] Hoekstra R, Fekkes D, Van De Wetering B, *et al*. Effect of light therapy on biopterin, neopterin and tryptophan in patients with seasonal affective disorder. Psychiatry Res, 2003, **120**(1): 37-42

[56] Lambert G, Reid C, Kaye D, *et al*. Effect of sunlight and season on serotonin turnover in the brain. Lancet, 2002, **360**(9348): 1840-1842

[57] Willeit M, Sitte H, Thierry N, *et al*. Enhanced serotonin transporter function during depression in seasonal affective disorder. Neuropsychopharmacology, 2008, **33**(7): 1503-1513

[58] Neumeister A, Willeit M, Praschak-Rieder N, *et al*. Dopamine transporter availability in symptomatic depressed patients with seasonal affective disorder and healthy controls. Psychol Med, 2001, **31**(8): 1467-1473

[59] Itzhacki J, Clesse D, Goumon Y, *et al*. Light rescues circadian behavior and brain dopamine abnormalities in diurnal rodents exposed to a winter-like photoperiod. Brain Struct Funct, 2018, **223**(6): 2641-2652

[60] Dienes K, Hazel N, Hammen C. Cortisol secretion in depressed, and at-risk adults. Psychoneuroendocrinology, 2013, **38**(6): 927-940

[61] Coleman G, Gigg J, Canal M. Postnatal light alters hypothalamic-pituitary-adrenal axis function and induces a depressive-like phenotype in adult mice. Eur J Neurosci, 2016, **44**(10): 2807-2817

[62] Legates T, Altimus C, Wang H, *et al*. Aberrant light directly impairs mood and learning through melanopsin-expressing neurons. Nature, 2012, **491**(7425): 594-598

[63] Hadlow N, Brown S, Wardrop R, *et al*. The effects of season, daylight saving and time of sunrise on serum cortisol in a large population. Chronobiol Int, 2014, **31**(2): 243-251

[64] Ostrin L A. Ocular and systemic melatonin and the influence of light exposure. Clin Exp Optom, 2019, **102**(2): 99-108

[65] Cardoso F, Gonzalez-Lima F, Gomes Da Silva S. Photobiomodulation for the aging brain. Ageing Res Rev, 2021, 70101415

[66] Khuman J, Zhang J, Park J, *et al*. Low-level laser light therapy improves cognitive deficits and inhibits microglial activation after controlled cortical impact in mice. J Neurotrauma, 2012, **29**(2): 408-417

[67] Salehpour F, Farajdokht F, Cassano P, *et al*. Near-infrared photobiomodulation combined with coenzyme Q for depression in a mouse model of restraint stress: reduction in oxidative stress, neuroinflammation, and apoptosis. Brain Res Bull, 2019, **144**: 213-222

[68] Hiles S, Baker A, De Malmanche T, *et al*. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: exploring the causes of heterogeneity. Brain Behav Immun, 2012, **26**(7): 1180-1188

[69] Eller T, Vasar V, Shlik J, *et al*. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry, 2008, **32**(2): 445-450

[70] Meyer J, Ginovart N, Boovariwala A, *et al*. Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. Arch Gen Psychiatry, 2006, **63**(11): 1209-1216

[71] Mohammed H, Khadrawy Y. Antidepressant and antioxidant effects of transcranial irradiation with 830-nm low-power laser in an animal model of depression. Lasers Med Sci, 2021. doi: 10.1007/s10103-021-03410-1

[72] De Freitas L, Hamblin M. Proposed mechanisms of photobiomodulation or low-level light therapy. IEEE J Sel Top Quantum Electron, 2016, **22**(3): 7000417

[73] Kafetzopoulos V, Kokras N, Sotiropoulos I, *et al*. The nucleus reuniens: a key node in the neurocircuitry of stress and depression. Mol Psychiatry, 2018, **23**(3): 579-586

[74] Sit D, Terman M, Wisner K. Light therapy and risk of hypomania, mania, or mixed state emergence: response to Benedetti *et al*. Am J Psychiatry, 2018, **175**(9): 906

[75] Sit D, Wisner K, Hanusa B, *et al*. Light therapy for bipolar disorder: a case series in women. Bipolar Disord, 2007, **9**(8): 918-927

[76] Tao L, Jiang R, Zhang K, *et al*. Light therapy in non-seasonal depression: an update meta-analysis. Psychiatry Res, 2020, **291**: 113247

[77] Min J, Min K. Outdoor light at night and the prevalence of depressive symptoms and suicidal behaviors: a cross-sectional study in a nationally representative sample of Korean adults. J Affect Disord, 2018, **227**: 199-205

[78] Blagonravov M, Bryk A, Goryachev V, *et al*. Bright light therapy increases blood pressure and changes the structure of circadian rhythm of melatonin secretion in spontaneously hypertensive rats. Bull Exp Biol Med, 2019, **168**(2): 214-218

[79] Avery D, Eder D, Bolte M, *et al*. Dawn simulation and bright light in the treatment of SAD: a controlled study. Biol Psychiatry, 2001, **50**(3): 205-216

[80] Wileman S, Eagles J, Andrew J, *et al*. Light therapy for seasonal affective disorder in primary care: randomised controlled trial. Br J Psychiatry, 2001, **178**: 311-316

[81] Terman M, Terman J. Controlled trial of naturalistic dawn simulation and negative air ionization for seasonal affective disorder. Am J Psychiatry, 2006, **163**(12): 2126-2133

[82] Flory R, Ametepe J, Bowers B. A randomized, placebo-controlled trial of bright light and high-density negative air ions for treatment of seasonal affective disorder. Psychiatry Res, 2010, **177**: 101-108

[83] Benedetti F, Colombo C, Pontiggia A, *et al*. Morning light treatment hastens the antidepressant effect of citalopram: a placebo-controlled trial. J Clin Psychiatry, 2003, **64**(6): 648-653

[84] Wu J, Kelsoe J, Schachat C, *et al*. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. Biol Psychiatry, 2009, **66**(3): 298-301

[85] Dauphinais D, Rosenthal J, Terman M, *et al*. Controlled trial of safety and efficacy of bright light therapy *vs*. negative air ions in patients with bipolar depression. Psychiatry Res, 2012, **196**(1): 57-61

[86] Chojnacka M, Antosik-Wójcińska A, Dominiak M, *et al*. A sham-controlled randomized trial of adjunctive light therapy for non-seasonal depression. J Affect Disord, 2016, **203**: 1-8

[87] Zhou T, Dang W, Ma Y, *et al*. Clinical efficacy, onset time and safety of bright light therapy in acute bipolar depression as an adjunctive therapy: a randomized controlled trial. J Affect Disord, 2018, **227**: 90-96

[88] Sit D, Mcgowan J, Wiltrout C, *et al*. Adjunctive bright light therapy for bipolar depression: a randomized double-blind placebo-controlled trial. Am J Psychiatry, 2018, **175**(2): 131-139

[89] Loving R, Kripke D, Shuchter S. Bright light augments antidepressant effects of medication and wake therapy. Depress Anxiety, 2002, **16**(1): 1-3

[90] Martiny K, Lunde M, Undén M, *et al*. Adjunctive bright light in non-seasonal major depression: results from clinician-rated depression scales. Acta Psychiatr Scand, 2005, **112**(2): 117-125

[91] Lieverse R, Van Someren E, Nielen M, *et al*. Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. Arch Gen Psychiatry, 2011, **68**(1): 61-70

Therapeutic and Neural Mechanisms of Light Therapy for Depression*

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Abstract Depression is a significant and persistent mood or low state of mind as the main performance of mental illness. Light therapy has attracted more and more attention due to its low side effects and low cost. Light therapy is a physical therapy method that uses artificial or natural light to prevent and cure diseases by using light of different duration and intensity. Animal and clinical trials have shown that light therapy can effectively relieve depressive symptoms. However, the neural mechanism of the antidepressant effect of light therapy is still not fully understood, and the application paradigm of light therapy is still controversial. This paper briefly introduces the clinical application light therapy in the seasonal depressive disorder (SDD), bipolar disorder (BD), sub-threshold depression (SD), major depressive disorder (MDD), perinatal depression (PPD), post stroke depression (PSD), and the underlying mechanisms of those effects of light therapy in anti-depression. Animal studies reveal that the effects of light on mood *via* intrinsically photosensitive retinal ganglion cells to perihabenular nucleus (ipRGC-PHb) pathway. A recent report demonstrated that activation of the disynaptic retina-vLGN/IGL-LHb pathway underlies the anti-depressive effects of light therapy. Monoamine neurotransmitter as well as cortisol are also involved in regulating depressive-like behaviors during light therapy. The current review provides potentially theoretical basis for the optimization and promotion of light therapy in anti-depression.

Key words depression, light therapy, ipRGC, emotional disorder

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