光疗在脑功能调控康复中的应用

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摘要　视网膜感光神经节细胞的发现开辟了一个全新的研究领域:光的非成像视觉功能。环境中的光对特定脑功能会产生广泛的影响。光作为一种重要的物理因子治疗方法,具有非侵入性、安全有效、成本低、毒副作用小、依从性高等特点,在耐受性和安全性方面具有明显优势,光疗在脑功能调控康复领域具有重要的临床价值。本研究系统梳理了光疗在情感障碍、认知功能障碍、睡眠障碍及疼痛领域康复中的应用,研究结果支持光疗对多种与大脑功能相关的疾病具有一定正向调节作用。但光疗在脑功能调控中的应用仍处于初步阶段,还存在一些不足之处,如光疗具体作用机制有待进一步阐明;较少开展光疗联合其他疗法的研究;光疗的长期临床效应有待观察。下一步研究还需解析光疗的神经机制,探讨建立靶向特定环路、高效调节脑功能的新型光疗范式;在传统康复治疗的基础上探讨光疗是否可以产生附加康复效应;加强光疗临床应用的长期随访,观察光疗是否具有长期效应,为光疗在脑功能调控的应用提供参考。

关键词　光疗;脑功能调控;情绪障碍;认知;睡眠;疼痛

环境中的光不仅参与形成视觉,还对情绪、认知、睡眠和疼痛等脑功能产生影响,这统称为光的非成像视觉功能(non-image forming vision,NIFV)[1-2]。光主要依赖视网膜上一类特殊的自身感光视网膜神经节细胞(intrinsic photosensitive retinal ganglion cells,ipRGCs)实现NIFV。ipRGCs能表达可感光的黑视蛋白,使机体在缺失视杆和视锥细胞的情况下也能对外界光刺激做出反应[3-4]。ipRGCs在包括人在内的多个物种中高度保守[5]。根据ipRGCs形态、对光的反应以及大脑特定区域的投射模式,ipRGCs可分为多个亚型,不同亚型ipRGCs可将光信息传递到不同脑区,介导光对不同脑功能的调节作用[6-7]。

本课题组前期系列基础研究和临床研究揭示了光调节脑功能的神经机制。前期研究采用临床随机对照试验结合神经影像学技术,发现了光疗缓解阈下抑郁的神经机制[8],与安慰剂组比较,光疗组背侧中缝核(dorsal raphe nucleus,DRN)与内侧前额叶(medial prefrontal cortex,mPFC)、腹侧被盖区(ventral tegmental area,VTA)和额上回(superior frontal gyrus,SFG)间的功能连接明显增强,且增强的VTA-SFG功能连接与抑郁缓解程度呈正相关关系[8]。外侧缰核(lateral habenula,LHb)至吻内侧被盖核(rostromedial tegmental nucleus,RMTg)通路可介导慢性压力对睡眠状态的影响作用,而光疗则可经由腹侧外膝体内部分γ-氨基丁酸(GABA)能神经元的介导进而降低慢性压力导致的LHb-RMTg通路过度激活,改善慢性压力致睡眠状态异常[9]。

光对NIFV产生短期的即时效应和长久的远期效应。充足光照有益于身心健康,而异常的光暴露与多种疾病密切相关。光疗是一种毒副作用小、成本低、依从性高的物理治疗方法,在耐受性和安全性方面具有明显优势。本研究探讨光疗在脑功能调控作用中的研究进展,为光疗在康复领域的临床应用提供参考。

1　光疗在情感障碍康复中的应用

早在20世纪80年代,光疗已经被应用于治疗季节性抑郁。1项Meta分析研究纳入19项随机对照试验(randomized controlled trials,RCTs),研究结果显示光疗治疗季节性抑郁的有效性[10]。有研究发现光疗对重度抑郁、双相抑郁、老年抑郁及产后抑郁等非季节性抑郁也有不同程度的治疗效果。LAM等[11]对122例重度抑郁患者进行随机对照双盲试验,光疗干预8周,采用蒙哥马利抑郁量表(Montgomery-Asberg depression rating scale,MADRS)的变化值评价疗效,结果表明光疗组和光疗/氟西汀联合治疗组的疗效均明显优于安慰剂组。GEOFFROY等[12]对光疗治疗重度抑郁症的研究进行系统评价,发现光疗和抗抑郁药同样有效,光疗联合抗抑郁药缓解重度抑郁症的疗效明显优于单独使用抗抑郁药。本课题组拓宽了光疗的临床应用场景,开展了光疗治疗142例阈下抑郁患者的RCTs,结果发现8周强白光治疗对阈下抑郁患者的抑郁和焦虑症状都具有明显缓解作用[13]。1项Meta分析研究纳入包含1 120例非季节性抑郁患者的23项RCTs,结果显示光疗对非季节性抑郁具有一定疗效[14]。另1项系统综述纳入7项RCTs,结果表明光疗与双相抑郁患者的抑郁症状改善明显相关,在临床反应方面有明

显优势[15]。

综上，光疗既可以作为单一疗法，也可以与药物等联合使用，对多种类型抑郁都有一定疗效。目前，多项国际抑郁症治疗的建议和指南提倡将光疗作为一种选择性的治疗方案。其中，加拿大情绪和焦虑治疗网络（Canadian Network for Mood and Anxiety Treatments，CANMAT）指南将光疗列为治疗季节性重度抑郁症的一级证据[16]，但也有研究提出光疗干预抑郁症临床证据的不确定性[17-18]。此外，值得注意的是，光疗抗抑郁的最佳干预范式尚未明确。虽有部分研究提示，每天少于60 min的光疗效果优于每天60 min以上的光疗，但有关光疗的最佳剂量仍未形成统一共识。关于光疗抗抑郁的参数选择，仍需要更多大样本、高质量的临床研究来支持。

2 光疗在认知功能障碍康复中的应用

越来越多研究显示，光疗可提高认知功能。本课题组前期系统综述纳入27项交叉设计研究和2项平行组设计研究，结果表明光疗对健康人的警觉性有积极影响[19]。KRETSCHMER等[20]对32例夜班工人进行光照疗法改善空间记忆的研究，结果提示强光组完成工作记忆任务的平均正确反应数明显高于对照组。SHISHEGAR和BOUBEKRI[21]研究表明，日常居家环境中的亮光照明能有效提高老年人的认知水平（包括执行功能、注意力和加工速度）。1项随机、双盲、安慰剂对照试验结果表明，蓝光可有效改善轻度创伤性脑损伤患者的执行功能[22]。1项多中心临床研究将189例高龄老人随机分配到强光组和昏暗组，并分别给予褪黑素或者安慰剂干预，结果发现强光可以明显提高早期痴呆症患者的一般认知功能，强光与褪黑素联合治疗可以提高患者的睡眠质量[23]。1项临床试验研究显示，光疗在改善造血干细胞移植幸存者的认知功能方面有一定效果[24]。有研究发现，40 Hz闪光能够通过激发小鼠脑中γ神经振荡而减少β淀粉样蛋白斑块，降低初级视觉皮层中tau蛋白磷酸化水平，从而达到提升小鼠认知功能以及治疗阿尔茨海默病的作用[25]。另有临床研究表明蓝光疗法有助于改善轻、中度阿尔茨海默病患者的一般认知功能[26]。本课题组前期研究从社区招募84例轻度认知障碍患者，随机分为光疗组或对照组，结果发现4周光疗可以有效改善轻度认知障碍患者一般认知功能、情景记忆、执行功能及视空间功能。但值得注意的是，1项系统综述纳入36项光疗干预认知功能障碍的RCTs，结果发现光疗对改善痴呆患者的睡眠、躁动和抑郁等症状具有良好效果，但是对认知功能的改善作用并不明显，推测其原因可能是痴呆患者的认知功能受损较严重，仅靠非药物干预的疗效非常有限[27]。研究结果还发现，光疗干预参数并不统一，如光照强度2 500～10 000 Lux，每次干预时长30 min～10 h，干预周期5 d～1年[27]。

综上，光疗可以有效提高健康人的警觉性，但是光疗改善其他认知功能（如记忆力、注意力和执行功能）的临床证据并不充分。关于光疗改善老年人认知功能的临床研究还处于起步阶段，既往研究多将光疗应用于治疗痴呆症。老年康复的核心理念是将干预窗口前移，光疗是否能有效改善轻度认知障碍和主观认知下降人群的认知功能，还有待更多高质量的RCTs提供支持。

3 光疗在睡眠障碍康复中的应用

光与睡眠密切相关[2]，是治疗睡眠障碍的潜在方法之一。1990年，光疗被应用于治疗睡眠时相延迟综合征（delayed sleep phase syndrome，DSPS），这种昼夜节律性睡眠障碍患者表现为入睡和起床时间远远晚于正常作息时间，研究结果发现，早晨2 h光照和晚上光照限制可以有效提前患者的昼夜节律[28]。20世纪80年代后，光疗被扩展应用于治疗其他睡眠障碍。2017年，中国睡眠研究会发布的《中国失眠症诊断和治疗指南》将光疗作为“指南”推荐等级用于治疗失眠症[29]。早晨明亮的光照可以使失眠患者的昼夜节律前移，有效缩短入睡时间并改善入睡困难[30]。1项纳入53项研究涉及1 154例参与者的Meta分析研究发现，光疗对一般睡眠问题有改善作用，但是对昼夜节律睡眠障碍的改善效果有限[31]。1项系统评价研究发现，亮光和褪黑素联合疗法在改善认知功能下降的老年群体睡眠质量方面优于单一疗法[32]。

此外，光疗还可以提高特殊人群的睡眠质量。1项双盲RCT以102例青少年为研究对象，提出一

种在睡眠期间光疗联合认知行为疗法的新型干预措施,可以有效提前入睡时间并增加夜晚睡眠时间[33]。1项在ICU进行的随机交叉临床试验研究发现,明亮的白光照明环境可以减少夜班护士的睡意[34];轮班制工作的护士接受强光治疗后可明显改善其失眠严重程度及焦虑症状[35]。产妇产后失眠是一种常见现象,有研究以分娩后4～12个月产妇为研究对象,结果发现暗光疗法可以改善失眠和睡眠障碍症状,其疗效与认知行为疗法相当[36]。另有临床研究表明,光疗可以改善帕金森病[37]、重度抑郁症[38]、乳腺癌化疗[39]、慢性失眠症[40]等患者的睡眠质量。

综上,光可以明显影响睡眠,包括睡眠行为和睡眠生理。目前较为一致的观点认为,白天光照对睡眠有益,而夜间光照则可能产生负面影响。光对睡眠的影响与光的干预参数密切相关,需要更多临床研究以探索光特性对睡眠的影响。光对睡眠的影响可以是间接的,也可以是直接的。首先,光可以通过影响节律对睡眠产生间接影响,位于下丘脑的视交叉上核(suprachiasmatic nucleus,SCN)是重要的昼夜节律中枢,环境中的光信息通过视网膜传递至SCN进而产生昼夜节律振荡[41]。其次,光可以通过影响内稳态调节睡眠[42]。再次,光通过NIFV可以直接调节和影响睡眠,但是光疗发挥作用的神经环路机制有待进一步解析。

4　光疗在疼痛康复中的应用

疼痛严重损害患者的日常功能、社会参与及生活质量。2019年全球疾病负担研究指出,腰痛的伤残寿命损失年(years lived with disabilities,YLDs)最高,其康复服务需求位于首位[43],腰痛成为康复医学领域亟待解决的重要科学问题。在临床实践中,疼痛的常用治疗方法包括阿片类镇痛药物、认知行为疗法、冥想和针灸等。然而,上述方法存在一定局限性。光疗是慢性疼痛的潜在治疗方法。1项前瞻性研究评估了阳光照射对接受脊柱手术患者的影响,结果显示患者在住院康复期间接受更多阳光照射可以减少压力、缓解疼痛,每小时服用止痛药减少21.95%[44]。BURGESS等[45-46]以纤维肌疼痛患者为研究对象,结果显示光疗可改善患者的功能并降低疼痛敏感性、疼痛程度及疼痛干扰。有研究以美国慢性腰痛退伍军人为研究对象,结果显示晨间亮光治疗是一种可行且可接受的治疗方法,能有效缓解慢性腰痛患者的疼痛程度和疼痛行为,降低疼痛敏感性,改善身体功能和睡眠质量[47]。有研究表明,亮光治疗与疼痛程度、疼痛干扰、负面影响和睡眠质量的平均水平变化有关,结果显示明亮光线治疗与参与者经历的"疼痛发作"减少有关[48]。1项针对非特异性背痛患者的RCT发现,强光组疼痛程度与抑郁症状明显改善[49]。

综上,光照可在一定程度上降低患者疼痛程度。光疗缓解疼痛的临床研究还处于起步阶段,既往研究提示光疗可以缓解偏头痛、术后疼痛、慢性腰痛等多种类型疼痛,但上述研究存在样本量小、缺乏双盲设计、缺少对照组等局限性。未来需要更多高质量的临床研究以增强光疗用于治疗疼痛的证据。

5　小　结

越来越多的临床证据表明,光疗对多种脑功能障碍都有一定正向调节作用,具体包括情感功能障碍、认知功能障碍、睡眠障碍和疼痛。见图1。但光疗在脑功能调控中的应用仍处于初步阶段,还存在一些不足之处。① 光疗具体作用机制有待进一步阐明:由于光疗具体机制不明确,光疗的临床应用面临困难,光疗的优化升级也无从下手。值得注意的是,不同的光疗范式对特定脑功能可能产生相反的影响。建立靶向光疗范式非常重要,这种范式可以根据不同视觉环路独特的光响应特性有效地激活特定的视觉环路。未来基础神经科学研究的开展将有助于开发改善神经和精神系统疾病的新型治疗策略。② 缺乏光疗联合其他疗法的研究:既往临床研究多探讨光疗的单独治疗效果,较少探讨光疗结合其他疗法(比如药物、运动、中医)的联合治疗效果,光疗作为一种脑调控新方法是否能在传统康复治疗的基础上产生附加康复效应有待进一步研究。③ 光疗的长期临床效应有待观察:多数研究探讨光疗的即时效应和短期效应,缺少长期的随访,光疗的长期效应尚未明确。下一步研究还需加强光疗临床应用的长期随访,为临床脑功能调控与康复方法的选择提供参考。

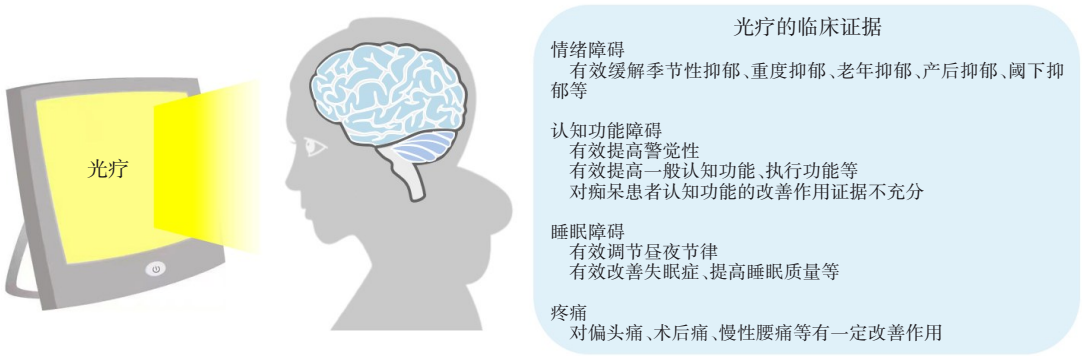

图1 光疗临床证据总结

Figure 1 Summary of clinical evidence for light therapy

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Application of Light Therapy in Brain Function Modulation and Rehabilitation

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ABSTRACT The discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs) has opened up a new field of research: the non-image forming visual (NIFV) of light. Light in the environment can have extensive effects on specific brain functions. As an important physical modality treatment method, light therapy is a novel intervention that has several strengths: non-invasive, safe, effective, low-cost, few adverse effects, and high compliance. It has clear advantages in terms of tolerance and safety. Light therapy has significant clinical values in the rehabilitation field of brain function modulation. This study systematically reviews the application of light therapy in the rehabilitation of mood disorders, cognitive dysfunction, sleep disorders, and pain. The results support that light therapy exerts a positive regulatory effect on various diseases related to brain function. However, the application of light therapy in brain function modulation is still in its early stage and there are several limitations. For example, the specific mechanisms of light therapy need to be further clarified, there is a lack of research on the combined use of light therapy with other treatments, and the long-term clinical effects remain to be observed. Future research should focus on analyzing the neural mechanisms of light therapy, establishing new intervention paradigms that target specific neural circuits and efficiently modulate brain function, and exploring whether light therapy can produce additional rehabilitative outcomes when combined with traditional treatments. Additionally, long-term follow-up studies are needed to observe the lasting effects of light therapy and to provide valuable insights for its application in brain function modulation.
KEY WORDS light therapy; brain function modulation; mood disorder; cognition; sleep; pain
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Application of "Hand−Brain Perception and Hand−Brain Movement" Theory in Upper Limb Rehabilitation after Stroke

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ABSTRACT Upper limb motor impairment is a major challenge for patients with stroke, and it is of great significance to explore more potent rehabilitation methods to improve functional recovery and quality of life. This study highlighted the important role of sensory function in promoting upper limb motor recovery, and interpreted the theory of "hand-brain perception and hand-brain movement". Guided by this theory, the research team has developed an effective five-step method of hand-brain perception training (sensory assessment, sensory education, sensory training, task-oriented training and sensory cognition), the brain-computer interface with hand-brain perception training paradigm, the hand-brain perception-mirror therapy training paradigm, and the other applications of the "hand-brain perception and hand-brain movement" theory. This study further delved into the relationship between the theory of "hand-brain perception and hand-brain movement" and the theory of "central-peripheral-central" closed-loop rehabilitation to provide reference and inspiration for the rehabilitation medical staff in the treatment of upper limb sensory and motor dysfunction after stroke.
KEY WORDS stroke; upper limb rehabilitation; motor function; sensory function; hand-brain perception; hand-brain movement
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