

综述

非侵入性脑刺激在抑郁障碍躯体症状治疗中的应用综述

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[摘要] 抑郁障碍的躯体症状与病程、缓解率、临床症状严重程度相关。目前一线治疗方法为药物治疗, 但药物的不良反应常与躯体症状相重叠。研究表明非侵入性脑刺激在抑郁障碍躯体症状的治疗上具有应用价值。该文综述了重复经颅磁刺激、经颅直流电刺激在抑郁障碍躯体症状治疗中的应用现状, 阐述了这两类非侵入性脑刺激技术对抑郁障碍患者疼痛、失眠等躯体症状的疗效与现有研究的不足, 并提出了后续研究的发展方向。

[关键词] 非侵入性脑刺激; 抑郁障碍; 躯体症状; 重复经颅磁刺激; 经颅直流电刺激

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Review of non-invasive brain stimulation for the treatment of somatic symptoms in major depressive disorder

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[Abstract] The somatic symptoms of major depressive disorder are related to the course of disease, remission rate and severity of clinical symptoms. At present, the first-line treatment is drug therapy, but the adverse effects of drugs often overlap with somatic symptoms. The studies have shown that non-invasive brain stimulation has application values in the treatment of somatic symptoms in major depressive disorder. This paper reviews the current status of repetitive transcranial magnetic stimulation and transcranial direct current stimulation in the treatment of somatic symptoms of major depressive disorder. It also discusses the efficacy of these two types of non-invasive brain stimulation techniques in the treatment of pain and insomnia in the patients with major depressive disorder, as well as the shortcomings of the existing research, and proposes the developing direction of future research.

[Key words] non-invasive brain stimulation; major depressive disorder; somatic symptom; repetitive transcranial magnetic stimulation (rTMS); transcranial direct current stimulation (tDCS)

抑郁障碍是常见的慢性复发性精神障碍, 具有高患病率、高复发率、高自杀率、高致残率和疾病负担沉重的特点。据估计, 2015年全球患抑郁障碍的人口比例为4.4%^[1]; 在中国, 抑郁障碍的终生患病率为6.8%, 12个月患病率为3.6%^[2], 平均复发率为39%^[3]。该疾病是造成非致命健康损失的最大因素, 也是自杀的最重要前兆^[1,4]。

除情绪与认知的改变, 约70%的抑郁障碍患者伴有躯体症状^[5], 而中国抑郁障碍伴躯体症状患者则更为常见^[6]。躯体症状与抑郁严重程度^[7], 及首发患者的自杀意念^[8]呈正相关, 并对抑郁障碍的病程具有负面影响^[7]。

中国抑郁障碍患者的主要躯体症状为失眠、难以用言语表达的身体不适、体质量减轻、食欲不振、循环系

统不适、头痛、性欲低下、胃肠系统不适和呼吸系统不适^[9]。药物治疗是目前针对抑郁障碍躯体症状的主要治疗手段, 特别是5-羟色胺-去甲肾上腺素再摄取抑制剂 (serotonin-noradrenaline reuptake inhibitor, SNRI) 已被证明对抑郁障碍残留症状具有较好的疗效^[10-11]; 但是抗抑郁药的不良反应很常见, 常与一些躯体症状相重叠, 如恶心、头痛、头晕、呕吐、腹泻等^[12], 甚至可以导致停药^[13]。而非侵入性脑刺激, 即不需要植入就可以进行的刺激^[14], 如重复经颅磁刺激 (repetitive transcranial magnetic stimulation, rTMS)、经颅直流电刺激 (transcranial direct current stimulation, tDCS)、经颅随机噪声刺激 (transcranial random noise stimulation, tRNS) 与经颅交流电刺激 (transcranial alternating current stimulation, tACS) 等, 具有价格低廉、不良反应小的优

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点^[15-16]；目前已有研究开始探讨rTMS、tDCS这两类非侵入性脑刺激技术对抑郁障碍躯体症状的疗效。而将tRNS、tACS应用于抑郁障碍的治疗仍处于初探阶段：有研究^[17-18]发现tRNS对抑郁障碍治疗效果不佳；仅有几项小样本研究^[19-20]证明tACS可能对抑郁障碍有效，能改善患者的情绪和认知^[21]，但尚未有研究专门探讨其对抑郁障碍躯体症状的影响。因此本文仅就rTMS、tDCS在抑郁障碍躯体症状治疗中的应用进行综述。

1 rTMS在抑郁障碍躯体症状治疗中的应用

1.1 rTMS概述

rTMS是一种非侵入性大脑刺激技术；在这种刺激技术中，变化的磁场会改变大脑神经回路的活动^[22]。高频rTMS (≥ 5 Hz) 被认为对大脑皮层有兴奋作用，而低频rTMS (≤ 1 Hz) 被认为有抑制作用^[22]。

rTMS被认为能显著改善成年人的抑郁症状，已被加拿大情绪和焦虑治疗指导小组(Canadian Network for Mood and Anxiety Treatments, CANMAT)成人抑郁障碍治疗指南^[16]认可为难治性抑郁障碍的一线治疗方法，常联合稳定剂量的药物进行治疗^[23-29]。在抑郁障碍患者左背外侧前额叶(left dorsolateral prefrontal cortex, L-DLPFC)采用高频rTMS治疗不仅可改善患者抑郁情绪，而且对躯体症状有显著影响^[24]；Zhang等^[29]对抑郁焦虑共病患者予以10次rTMS后，发现rTMS可改善青少年、成人、老年患者的躯体和心理焦虑，老年患者躯体焦虑的改善显著优于心理焦虑的改善，其中躯体焦虑通常表现为躯体症状^[30]，如头痛、失眠和疲劳。rTMS在改善抑郁障碍患者的躯体症状上具有潜力，特别是疼痛、睡眠、食欲和体质量问题等方面。

1.2 rTMS对抑郁障碍疼痛症状的治疗作用

抑郁和疼痛紧密关联^[31]，同时发生的概率为30%~60%^[32]。世界卫生组织的资料显示，超过75%的抑郁障碍患者抱怨有疼痛相关的症状，如头痛、胃痛、颈部疼痛、背痛^[33]，而疼痛与抑郁障碍的治疗效果、缓解时间、患者的生活质量有关^[34]。

虽然目前仅有少量研究关注rTMS对于抑郁障碍患者疼痛的改善作用，但这些研究均发现rTMS能改善患者疼痛症状。如Phillips等^[28]对患者L-DLPFC采用rTMS连续治疗6周，难治性抑郁障碍患者的疼痛症状得到改善。一项案例报告^[35]显示，在rTMS治疗过程中，抑郁障碍

患者的头痛明显减少，但停止治疗后又恢复到基线水平，之后继续接受rTMS作为维持治疗时，患者头痛缓解的积极效果得以维持。

1.3 rTMS对抑郁障碍睡眠症状的治疗作用

睡眠质量差、失眠等常是抑郁障碍患者的主诉，伴有睡眠问题的患者表现出更严重的抑郁程度、更大的治疗阻力与更高的复发风险^[36]。

对于rTMS能否改善抑郁障碍患者的睡眠症状，目前尚无共识。一些研究发现，rTMS对抑郁障碍患者的睡眠症状没有影响。如Kaur等^[25]给予患者L-DLPFC高频rTMS治疗4周，发现rTMS对患者的客观睡眠-唤醒没有影响。Antczak等^[24]给予抑郁障碍患者L-DLPFC 20次高频rTMS治疗，发现rTMS对客观睡眠质量影响不显著。Nishida等^[26]通过先给予患者右背外侧前额叶(right dorsolateral prefrontal cortex, R-DLPFC)低频rTMS，再给予L-DLPFC高频rTMS，共治疗10次，发现患者客观睡眠有改善的趋势，但rTMS对睡眠时长(total sleep time, TST)、睡眠效率(sleep efficiency, SE)和觉醒(wake after sleep onset, WASO)的影响没有统计学意义。

另一些研究则认为rTMS能改善抑郁障碍患者的睡眠症状，认为在rTMS治疗后，患者从睡眠障碍中恢复的概率更大。Pellicciari等^[27]给予患者10次rTMS治疗后，在其快速眼动睡眠期间观察到L-DLPFC的 α 波(8~12 Hz的平稳脑电波，在觉醒状态时产生)减少。Antczak等^[24]发现rTMS对患者的主观睡眠质量(入睡时长、TST、早醒、失眠)影响显著。

有学者在研究过程中发现睡眠症状的测量方式不一致，得到的结论也可能不同。Nishida等^[26]分别使用匹兹堡睡眠质量指数(Pittsburgh Sleep Quality Index, PSQI)和爱泼沃斯嗜睡量表(Epworth Sleepiness Scale, ESS)进行评估发现，经rTMS治疗后PSQI显著改善，而ESS无显著改善。

睡眠由多个维度组成，包括TST、SE、WASO等^[26]，rTMS可能对特定的睡眠指标有效。如Sonmez等^[23]给予青少年难治性抑郁障碍患者L-DLPFC 30个疗程的高频rTMS(6~8周)，使用青少年抑郁症状快速量表(17个条目)自评版[The Quick Inventory of Depressive Symptomatology-Adolescent (17-Item)-Self Report, QIDS-A₁₇-SR]的3个条目评估失眠症状，用QIDS-A₁₇-SR的1个条目评估嗜睡症状，发现rTMS对患者的失眠症状无影响，对其嗜睡症状有影响。

1.4 rTMS对抑郁障碍食欲和体质量问题的治疗作用

目前rTMS对抑郁障碍患者食欲或体质量影响的相关研究数量仍较少,仅有一篇文献对此有报道,显示可喜的结果。Jaššová等^[37]通过在抑郁障碍患者的L-DLPFC上给予高频rTMS,使用宗氏抑郁自评量表第5题和第7题进行评估,发现rTMS可以改善抑郁症状及相关的行为因素(食欲和体质量趋于稳定)。

2 tDCS在抑郁障碍躯体症状治疗中的应用

2.1 tDCS概述

tDCS是一种无创神经调节技术^[38],它使用2个头皮表面电极给予大脑皮层低强度的直流电(一般为1~2 mA),改变神经元的膜电位与自发去极化的速率,使阳极区域变得低极化,阴极区域变得超极化^[39]。一项基于系统回顾和meta分析的临床指南^[40]指出,将阳极置于L-DLPFC的tDCS对改善抑郁障碍确实有效,被列为A级推荐。与rTMS相比,tDCS具有体积小、成本低、操作便捷^[16]的优点,在抑郁障碍治疗上具有巨大价值。

目前仅有少量研究探讨了tDCS对抑郁障碍躯体症状的疗效,部分研究未发现tDCS对此类症状具有改善作用。如Brunoni等^[41]在患者(部分患者服用苯二氮草类药物,其他患者从未服用过药物或在药物洗脱期后参与研究)的DLPFC上给予10次tDCS治疗,用蒙格马利抑郁评定量表的第3~5题评估,发现tDCS对TST减少、食欲下降这两大躯体症状没有显著改善作用。这可能是由于躯体症状需要更长的时间才能对治疗产生反应^[42],而目前将tDCS应用于抑郁障碍研究^[43-45]所实施刺激的时间较短,多集中在2~3周(10~15次)。同时,上述研究仅从量表的个别条目对躯体症状进行评估,无法完全确定tDCS对抑郁障碍患者躯体症状的疗效,尤其是疼痛与睡眠方面。

2.2 tDCS对抑郁障碍疼痛症状的治疗作用

虽然目前尚未有研究专门探讨tDCS对抑郁障碍患者疼痛症状改善的疗效,但tDCS在这方面具有应用潜力。一项基于系统回顾和meta分析的临床指南^[40]指出,在初级运动皮层(primary motor cortex, M1)上给予阳极tDCS可能对减轻神经性疼痛、纤维肌痛、偏头痛有效,被列为B级推荐。同时,有研究^[46-47]发现在DLPFC上施加tDCS也能改善纤维肌痛和偏头痛。而疼痛和抑郁常存在共病,tDCS能在改善疼痛的同时,改善抑郁症状。一

项案例报告^[48]显示,在脑卒中患者的R-DLPFC上给予阳极tDCS,在对侧眶上区给予阴极tDCS,连续2周(5次/周)给予2 mA、持续20 min的刺激后发现,患者的抑郁症状、卒中后疼痛均改善;然而干预3周后患者症状复发(抑郁症状、卒中后疼痛恶化),继续给予1周(7次/周)2 mA强度的周期性刺激,发现患者的抑郁症状改善,疼痛完全消失。Khedr等^[49]对纤维肌痛患者的M1施加10次tDCS后发现,tDCS能改善患者的抑郁情绪与疼痛症状。

2.3 tDCS对抑郁障碍睡眠症状的治疗作用

虽然目前仅有少量研究探讨tDCS对抑郁障碍患者睡眠改善的疗效,但均显示出可喜的结果。对照研究^[50]发现2周的tDCS治疗对患者主观睡眠质量和睡眠持续性有显著的改善作用,且均优于伪刺激。Zhou等^[51]的研究证实双侧阳极tDCS对抑郁障碍伴睡眠问题患者(治疗期间服用固定剂量的艾司西酞普兰和佐匹克隆)的睡眠质量和抑郁水平有改善作用;与伪刺激组相比,患者PSQI总分、TST、SE之间差异有统计学意义。同时,患者基线的睡眠水平可预测其对tDCS的应答。如Rezaei等^[52]发现,对tDCS无应答的抑郁患者睡眠问题更严重,睡眠问题可作为对tDCS治疗是否有应答的预测因素。因此,tDCS在抑郁障碍患者睡眠症状的改善上具有应用潜力。

3 结语与展望

目前对于抑郁障碍的诊疗多关注情感与认知的改变,较少关注躯体症状,但躯体症状的改善对抑郁障碍症状的缓解、预后具有重要意义。非侵入性脑刺激技术,如rTMS、tDCS对抑郁障碍患者躯体症状的改善具有潜力,特别是疼痛、睡眠方面。

rTMS在治疗抑郁障碍患者的疼痛方面,虽然目前已有研究证明,作用于DLPFC的rTMS能改善抑郁障碍患者的疼痛症状^[28,35],且作用于L-DLPFC的rTMS被认为具有明确的抗抑郁作用(A级推荐)^[53],但尚不清楚rTMS的抗抑郁作用与疼痛减少的关系。疼痛感知是由一个复杂的大脑区域和回路网络(疼痛矩阵)控制,包括认知、情绪和情感要素,其中DLPFC是参与疼痛感知的重要区域^[54];而抑郁障碍患者大脑DLPFC存在皮层兴奋性失衡,即相较于健康人群,患者L-DLPFC兴奋性较低,而R-DLPFC较高^[55]。因此,刺激DLPFC区域可能可以在改善患者疼痛症状的同时改善其抑郁症状。同时,疼痛(头皮疼痛、头痛等)为rTMS可能的不良反应,是否

会影响抑郁障碍患者对疼痛的认知应被纳入考虑范围。

rTMS在治疗抑郁障碍患者睡眠方面,目前尚无共识。首先,这可能是因为睡眠变量包括多个维度,且研究者采用多种不同的方式对睡眠进行测量,造成测量结果的不一致。其次,已有研究缺乏对于被试的严格控制,将rTMS作为药物之外的辅助治疗方法,即在rTMS治疗过程中,被试仍服用稳定剂量的抗抑郁药和/或催眠药物,但较少有研究对药物的类型、服药时间长短进行控制,因此较难判断是药物还是rTMS对患者的睡眠产生了效果。最后,睡眠变量易受昼夜节律的影响^[56],但很少有研究将每日采用rTMS的开始时刻纳入考虑范围,刺激开始时刻的不一致可能会影响rTMS的治疗效果。

tDCS在治疗抑郁障碍的疼痛方面,虽然目前尚无专门研究,但在L-DLPFC上施加tDCS已被认为对抑郁障碍治疗明确有效(A级推荐)^[40],且具有显著镇痛(偏头痛、纤维肌痛)的作用^[46-47]。有研究^[48-49]指出tDCS能在改善患者抑郁情绪的同时改善其疼痛症状。DLPFC在调节疼痛中起着关键作用^[57];而目前将tDCS应用于抑郁障碍的治疗中,多选择L-DLPFC为阳极刺激点以增强其兴奋性,选择R-DLPFC或右侧眶额叶为阴极刺激点以抑制其活性^[58]。因此,作用于DLPFC的tDCS在改善抑郁障碍患者疼痛症状上具有潜力。

tDCS在治疗抑郁障碍睡眠方面的研究发现,tDCS能

改善抑郁障碍患者的主观睡眠质量和睡眠持续性^[50],能在改善患者抑郁情绪的同时改善其睡眠^[51],且对tDCS有应答的患者睡眠改善情况更好^[52]。侧眶额皮层、楔叶及DLPFC等脑区共同构成了抑郁与睡眠质量关系的脑神经网络基础,这些脑区间的连接增强可能使得相关个体长期处于某些负面情绪中,进而导致睡眠质量下降^[59]。由于tDCS对抑郁障碍的治疗多采用DLPFC作为刺激靶点,而DLPFC又是抑郁与睡眠质量关系的重要脑区,因此,tDCS是否能改善抑郁障碍患者的睡眠是未来值得深入探讨的方向。

总体而言,目前将rTMS、tDCS应用于抑郁障碍患者躯体症状治疗的相关研究仍较少,研究的样本量较小,缺乏对rTMS、tDCS的参数(刺激靶点、刺激时长、刺激频率、刺激时间)及其他治疗方案使用的严格控制,而且采用不同的主客观方法测量躯体症状。虽然rTMS、tDCS在治疗抑郁障碍患者的疼痛、失眠等躯体症状中具有一定潜力,但尚不清楚其背后的作用机制。同时,由于SNRI类药物已被证明对抑郁障碍患者躯体症状的改善效果较好^[10-11],因此后续研究可扩大样本量,设立SNRI类药物对照组,在rTMS、tDCS治疗的同时控制其他干扰因素,通过磁共振成像、脑电图等方式研究rTMS、tDCS应用于抑郁障碍患者躯体症状治疗的效果及作用机制。

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