

经颅直流电刺激在孤独症谱系障碍 康复中的应用进展

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摘要: 孤独症谱系障碍(ASD)是一种以社交障碍、狭隘兴趣和重复刻板行为为特征的神经发育障碍性疾病, 临床症状多变且治疗难度大。经颅直流电刺激(tDCS)作为一种非侵入性的脑刺激方式, 通过调节局部皮层兴奋性改善 ASD 患者的临床症状, 其机制涉及纠正异常的兴奋抑制比(E/I)、调节脑代谢物水平、优化大脑功能连通性及改善脑血流动力学等。本文综述 tDCS 在 ASD 治疗中的靶点选择、作用机制及临床疗效, 并探讨其在 ADHD、抑郁症等神经精神疾病中的扩展应用及安全性。

关键词: 孤独症谱系障碍; 经颅直流电刺激; 康复

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Advances in transcranial direct current stimulation for autism spectrum disorder rehabilitation

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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication deficits, restricted interests, and repetitive behaviors, exhibiting variable clinical manifestations and significant treatment challenges. As a non-invasive brain stimulation technique, transcranial direct current stimulation (tDCS) can alleviate clinical symptoms in individuals with ASD by modulating local cortical excitability. The underlying mechanisms involve correcting the abnormal excitation/inhibition (E/I) ratio, regulating levels of cerebral metabolites, optimizing functional brain connectivity, and improving cerebral hemodynamics. This article reviews the target selection, mechanisms of action, and clinical efficacy of tDCS in the treatment of ASD. It also explores its extended applications in other neuropsychiatric disorders such as ADHD and depression, as well as its safety profile.

Keywords: autism spectrum disorder; transcranial direct current stimulation; rehabilitation

孤独症谱系障碍(autism spectrum disorder, ASD)是一种神经发育障碍性疾病,其特征是社会情感功能和相关行为受损,如社交障碍、狭隘兴趣和重复刻板行为等^[1]。2020 年调查数据显示,我国 ASD 儿童患病率为 0.7%(男女比例为 4.1:1),患者数量全球最多^[2]。美国 ASD 的患病率 20 年增长 4 倍,8 岁儿童患病率达 1/36^[3]。然而,传统康复治疗依赖人力且效果有限,药物疗效亦不显著。

近年来,经颅直流电刺激(transcranial direct current stimulation, tDCS)作为一种简单、无痛、可重复性高、副作用小的技术,在 ASD 治疗过程中展现出显著的临床潜力。此外,该技术在多种神经精

神疾病的干预中也表现出广泛的应用前景,包括注意缺陷多动障碍(attention deficit/hyperactivity disorder, ADHD)^[4-5]、抑郁症^[6-7]、帕金森病(Parkinson's disease, PD)^[8]、以及阿尔茨海默症(Alzheimer's disease, AD)^[9]等。本综述将聚焦于 tDCS 在改善 ASD 核心症状的临床应用及其具体机制,为未来研究和临床应用提供参考。

1 经颅直流电刺激治疗孤独症谱系障碍的常用靶点

1.1 额叶皮质 背外侧前额叶皮质(dorsolateral prefrontal cortex, DLPFC)是治疗 ASD 最常用的靶点。DLPFC 是大脑中参与运动控制、调节和抑制的

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最高皮质区域之一,在社会认知、情绪调节过程中发挥重要作用。研究表明,右侧眶上区阳极/左侧 DLPFC 阴性的 tDCS 结合认知训练可提升 ASD 患者的社会功能^[10];10 次左侧 DLPFC 阳极/右侧 DLPFC 阴极刺激能改善临床症状、心理理论能力和情绪调节能力,效果可以维持 1 个月^[11];而左侧 DLPFC 阴极刺激可增强患者社会功能并显著减少刻板行为^[12]。研究证实 DLPFC-tDCS 联合感觉统合训练可改善 ASD 患者的认知、情绪及感觉统合能力^[13],结合音乐训练还能缓解学龄前儿童 ASD 核心症状与睡眠障碍^[14]。此外,ASD 患者腹内侧前额叶皮质(ventromedial prefrontal cortex, vmPFC)的兴奋性明显升高^[15],该区域与社会行为受损有关^[16],对该区域施加 tDCS 能显著改善心理理论和社会功能^[17]。最新临床研究方案及疗效评估见表 1。

1.2 颞顶叶交界处 右侧颞顶叶交界处(tempor-

oparietal junction, TPJ)与大脑广泛区域之间存在异常的功能连接,这种异常与 ASD 的社交障碍相关^[18]。对右侧 TPJ 施加阳极 tDCS 后,可提高对自发性微表情的识别^[19]。对右侧 TPJ 区域施加连续 4d(30min/d)的 tDCS 可以提升 ASD 患者的情绪识别能力^[20]。此外,成人 ASD 患者在接受认知训练结合靶向右侧 TPJ 的阳极 tDCS 治疗后,社会认知和情绪处理能力得到显著改善^[21]。

1.3 顶点 临床研究表明,以顶点(Cz)为阳极的高精度经颅直流电刺激(high-definition transcranial direct current stimulation, HD-tDCS)具有可行性和安全性,并能有效地改善 ASD 患儿的社交功能障碍^[22]。机制研究发现,以 Cz 为中心的 HD-tDCS 可能通过激活副中心小叶^[23]和增加以副中心小叶为枢纽的社会脑网络的功能连通性来提高 ASD 儿童感知、识别和社交互动的准确性^[24]。

表 1 tDCS 治疗 ASD 的常用类型、治疗参数及疗效

Tab. 1 Common tDCS protocols, treatment parameters, and efficacy in ASD therapy

类型	刺激区域(阳极)	刺激区域(阴极)	样本量(个)	电流(mA)	疗程	tDCS 疗效	参考文献
传统 tDCS (一个阴极, 一个阳极)	右侧眶上区	左侧 DLPFC	41	1.5	2 周,5 次/周, 20min/次	提升社会功能,增加 PFC 的功能连通性	[10]
	左侧 DLPFC	右侧 DLPFC	32	1.5	5 周,2 次/周, 15min/次	改善临床症状、心理理论 和情绪调节	[11]
	DLPFC	对侧 DLPFC	12	1.5	单次	提升工作记忆	[25]
	右侧 vmPFC	左侧 DLPFC	60	1.5	2 周,5 次/周, 20min/次	提升社会功能,提高执行 任务期间的信息处理效率	[12]
	左侧 DLPFC	右侧眶上区域	37	1.5	4 周,3 次/周, 21min/次	减轻症状严重程度	[26]
	vmPFC/r-TPJ	左肩	16	1.0	单次,20min	改善心智理论	[17]
双阳极 tDCS	右侧 TPJ	同侧三角肌上方	6	2.0	单次,30min	改善语言流畅度	[21]
	FC1,FC2	双侧眶上区域	50	1.0	2 周,5 次/周, 20min/次	提高社交能力,改善健康 状况	[27]
HD-tDCS	Cz	FC1,FC2,CP1,CP2	45	2.0	3 周,5 次/周, 20min/次	改善社交障碍,减少刻板 行为	[22]

注:FC1、FC2、CZ、CP1、CP2 均为国际 10-10 脑电图系统电极放置位置名称。

2 经颅直流电刺激作用机制

tDCS 的作用机制尚不明确,现有报道涉及:纠正异常的兴奋抑制比(excitation/inhibition ratios, E/I)、调节脑代谢物水平、优化大脑功能连通性及改善脑血流动力学等,具体如下。

2.1 纠正 E/I 失衡 研究指出,认知情感处理相关的局部神经网络中 E/I 失衡会干扰大脑信号的传导,影响整体功能^[28]。E/I 平衡指的是局部神经环路中兴奋性和抑制性突触输入的动态平衡状态,该平衡失衡可能由谷氨酸能信号转导增加或 γ -氨基丁酸(gamma-aminobutyric acid, GABA)信号转导减

少引起。动物模型^[29]和临床研究^[30-31]的结果都表明,ASD 患者的 E/I 比值高于健康对照组。阳极和阴极 tDCS 可以选择性地减少 GABA 和谷氨酸合成,从而分别增强和抑制受刺激大脑区域的神经元兴奋性^[32]。DLPFC-tDCS 联合认知训练能降低 ASD 患者社会认知回路 θ 波段的 E/I 比率,优化大脑信息处理效率^[12]。

2.2 调节脑代谢物水平 ASD 患者脑代谢物水平异常。N-乙酰天门冬氨酸(N-acetylaspartate, NAA)主要存在于神经元内,执行功能相关大脑区域的 NAA 浓度降低可能与 ASD 患者的社交沟通障碍有关^[33]。胆碱(choline, Cho)是人体必需的营养

养素,可反映神经元连接水平。研究显示,ASD 患儿 DLPFC 中 NAA 浓度降低而 Cho 浓度显著增加^[34],成年患者仅表现为 NAA 浓度降低^[33]。研究显示,连续 5d 对 ASD 患儿左侧 DLPFC 施用 1mA 阳极 tDCS 刺激 20min 后,左侧 DLPFC 中 NAA 浓度显著上升,Cho 下降,且孤独症治疗评估量表 (Autism Freatment Evaluation Checklist, ATEC) 评分改善与这些代谢物变化正相关^[35]。

2.3 优化大脑功能连通性 研究发现 6~12 岁 ASD 儿童社会功能相关脑区与双侧中心旁小叶、辅助运动区、中央前回、中央后回、内侧和副扣带回的功能连通性降低^[36]。此外,ASD 患者的 PFC 显示出异常的功能连接,该区域是处理自我相关信息的关键节点^[37]。tDCS 能够改善 ASD 患者大脑的功能连接:41 名 ASD 患者接受阴极作用于 DLPFC 的 tDCS 治疗后,试验组的社会功能显著提升,右侧 PFC 的静息态功能连接 (resting-state functional connectivity,rsFC)增强,且两者呈正相关^[10]。Meta 分析证实前额叶 tDCS 能增强 rsFC 并改善临床症状,且 rsFC 变化与电场强度正相关^[38]。

2.4 改善脑血流动力学 据 MRI 结果分析,ASD 儿童颞叶、海马、壳核等脑区脑血流量低于健康儿童^[39]。研究表明,阳极的 tDCS 可以诱导小动脉的扩张并调节毛细血管内的血流速度,增强血流灌注改善脑区的微循环^[40]。根据 Ghafoor 等^[41]报道,tDCS 可以增加左侧和右侧 PFC 的血流量并改善 ASD 患者的临床表现。

3 经颅直流电刺激在其他神经疾病中的应用

3.1 注意缺陷多动障碍 ADHD 是一种以注意力缺陷、冲动控制障碍及执行功能异常为特征的神经发育性疾病^[42]。Meta 分析显示,DLPFC 是 tDCS 治疗 ADHD 最常用靶点,可改善工作记忆、注意力、认知灵活性等^[4]。近期研究发现,目标靶点为 vmPFC 的 tDCS 可以显著地改善 ADHD 的热执行功能障碍 (例如,风险决策和延迟折扣)^[43],而 10d 的多通道 tDCS 方案可以改善 ADHD 患者的干扰控制并提高工作记忆的准确性,疗效持续≥4 个月^[44]。最新的临床研究见表 2。

表 2 tDCS 对于不同类型疾病的临床应用
Tab. 2 Clinical applications of tDCS in different types of diseases

疾病类型	刺激区域 (阳极)	刺激区域 (阴极)	样本量 (个)	电流 (mA)	疗程	疗效评估	参考文献
ADHD	右侧 DLPFC	左侧 DLPFC	29	2.0	4 周,7 次/周, 30min/次	提高注意力	[45]
	右侧 DLPFC	左侧 DLPFC	22	2.0	5 次	改善认知功能	[46]
	左侧 DLPFC	右侧 vmPFC	20	1.0	单次,15min	改善热执行功能(例如,风险决策和延迟折扣)	[43]
	F6-F8 之间	AFz-P7 之间	34	1.0	2 周,5 次/周, 20min	增强干扰控制能力,提高工作记忆准确性	[44]
抑郁症	左侧 DLPFC	右侧 OFC	63	2.0	2 周,5 次/周, 30min/60min	改善抑郁症状,60min 的刺激更能改善焦虑情绪	[47]
	左侧 DLPFC	右侧 DLPFC	80	2.0	2 次/d, 20min	提升认知功能和社会心理功能,改善焦虑症状	[48]
	左侧 DLPFC	Fp1,F2,C3,F7	50	2.0	2 周,7 次/周, 20min	降低抑郁严重程度	[49]
PD	C3/C4	Fp1/Fp2	22	2.0	2 周,5 次/周, 20min	减轻 PD 相关疼痛,增强下行疼痛抑制	[8]
	小脑水平后颅窝	右臂	17	2.0	2 周,5 次/周, 20min	增强运动控制,有更好的姿势稳定性	[50]
AD	左侧 DLPFC	右侧 DLPFC	26	2.0	2 次/d,20min	增强认识控制和情景记忆能力	[51]
	左侧 DLPFC	Fp2	33	2.0	10 次,20min	提升认知功能、即时和延迟记忆以及学习能力	[9]
	右侧颞下回	F6,FT8,C4,C6	229	1.5	10min	增强认知灵活性	[52]

注:AFz、Fp1、Fp2、C3、C4、C6、FT8、F2、F6、F7、F8、P7 均为国际 10-10 脑电图系统电极放置位置名称。

3.2 抑郁症 tDCS 被证明是一种可以减少自杀意念和改善抑郁症状的有效方式^[7]。短期(2 周)应用于 DLPFC 的 tDCS 可以显著改善抑郁症患者快感

缺乏,长期(8 周)应用于 DLPFC 和眶额叶皮层 (orbitofrontal cortex,OFC)的 tDCS 可以改善抑郁症患者的社会功能^[6]。

3.3 帕金森病 tDCS 可以改善 PD 患者的运动症状和非运动症状。Meta 分析提示 tDCS 可以改善 PD 患者姿势步态障碍^[53]。靶点为小脑和 M1 区的阳极 tDCS 可通过小脑抑制和调节运动皮质兴奋性来改善 PD 患者的异动症^[54]。阳极靶点为 DLPFC 的 tDCS 可提升刺激脑区局部皮层的兴奋性,改善 PD 患者的执行功能和语言流畅性^[55]。

3.4 阿尔茨海默病 Meta 分析表明,刺激颞叶、电流密度 $\geq 0.08\text{mA}/\text{cm}^2$ 的 tDCS 可改善 AD 患者的整体认知能力^[56]。研究报道指出,33 名 AD 患者在接受 10 次以 DLPFC 为阳极的 tDCS 治疗后,其一般认知功能、即时和延迟记忆以及学习能力均有显著提高^[9]。

4 经颅直流电刺激的安全性

tDCS 安全性总体良好,临床研究中仅报告轻微的不良反应(如短暂性头皮红斑^[22]、瘙痒^[10]),通常在刺激后 15min 内自行缓解。但个案报告显示特殊人群存在风险:1 例 4 岁有癫痫病史的患儿在第 3 次刺激后 4h 出现部分性癫痫发作^[57],1 例 13 岁儿童在应用 tDCS 后 1 周内首次出现全身强直阵挛发作^[58]。因此,tDCS 临床治疗 ASD 仍需大规模临床验证。

tDCS 作为一种操作简便、无痛、可重复性强且副作用小的非侵入性技术,在 ASD 的康复治疗中展现出显著潜力。其刺激靶点和形式多样,安全性较高,可能为不同临床亚型的 ASD 患者和多种神经精神疾病提供个体化治疗的可能性。然而,由于目前缺乏大样本、双盲对照的临床试验,tDCS 的临床应用仍需通过进一步的科学研究来验证疗效并阐明机制。

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