

经颅直流电刺激治疗卒中后认知障碍的相关研究进展

刘员辰,张立新*

中国医科大学附属盛京医院,辽宁 沈阳 110000

* 通信作者:张立新, E-mail: zhanglx@sj-hospital.org

收稿日期:2023-11-17;接受日期:2024-01-07

基金项目:国家重点研发计划项目(2020YFC2005700,2020YFC2007600)

DOI:10.3724/SP.J.1329.2024.03013

开放科学(资源服务)标识码(OSID):



摘要 卒中后认知障碍(PSCI)是指脑卒中后出现认知功能下降,严重影响患者的生活质量及生存时间。与其他神经系统疾病引起的认知障碍相比,可预防性和可治疗性是PSCI的重要特点,因此早期干预尤为重要。经颅直流电刺激(tDCS)属于非侵入性脑刺激技术,具备安全性高、疼痛感低等优点,是PSCI的一种有效神经康复治疗手段。PSCI的tDCS治疗方案通常为1~2 mA的刺激强度作用于背外侧前额叶皮层20~30 min。刺激部位通常选择背外侧前额叶,也有学者证实其他刺激区域的有效性,如双侧M1区、右顶叶皮层等。tDCS通过影响神经递质(如星形胶质细胞中的钙离子和 γ -氨基丁酸)、神经元的状态、脑血流量以及大脑功能区域的连接发挥疗效,改善认知功能。tDCS不仅可产生即刻的促进效应、刺激后约1 h有效的后效应,而且具有长时程增强(LTP)和长时程抑制(LTD)效应。因此,在临床应用tDCS时应把握好治疗时机。目前认知障碍的各种传统治疗手段(如药物治疗、认知训练、虚拟现实技术、针灸等)虽各有所长,但仍存在着药物不良反应、治疗时间长、恢复慢等问题。为弥补单独应用tDCS的局限与不足、达到更佳的治疗效果,可选择在tDCS刺激的同时或1 h内联合应用其他认知康复手段。本文旨在综述tDCS及其他认知康复方法在PSCI方面的相关研究进展,藉此为PSCI全面康复提供治疗经验和参考依据。

关键词 卒中后认知障碍;脑卒中;经颅直流电刺激;联合治疗;时机

世界中风组织(World Stroke Organization, WSO)发布的“2022年全球中风概况”^[1]指出,脑卒中是世界上第二大死亡和第三大残疾原因,全球每年新增病例超过1 300万。脑卒中患者常伴有功能缺陷^[2],如运动无力、感觉功能障碍、言语障碍、吞咽困难、单侧空间忽略、认知功能障碍和情绪障碍等^[3-5]。虽然目前有效的急性期治疗措施改善了脑卒中在全球范围内的不良趋势^[6],但卒中后认知障碍(post-stroke cognitive impairment, PSCI)的发生率仍然很高^[7],表现为记忆力、注意力、思维、知觉的障碍和失用失认等。此外,PSCI也影响着患者的自主活

动,导致运动和学习能力减退,并与致残率和复发率密切相关^[8-9],给患者和护理人员带来了巨大负担^[10-11],必须早期识别、管理和干预。临床上迫切需要可行的治疗方案减缓PSCI的进展,争取达到理想的康复效果。

传统认知疗法存在难以突破的治疗瓶颈,比如患者配合度低、短期效果甚微等。便捷简单的非侵入性脑刺激技术如经颅直流电刺激(transcranial direct current stimulation, tDCS)为治疗PSCI提供了新思路和新方向。将tDCS应用于PSCI的康复治疗方

引用格式:刘员辰,张立新. 经颅直流电刺激治疗卒中后认知障碍的相关研究进展[J]. 康复学报, 2024, 34(3):304-310.

LIU Y C, ZHANG L X. Research progress in transcranial direct current stimulation therapy for cognitive impairment after stroke [J]. Rehabil Med, 2024, 34(3): 304-310.

DOI:10.3724/SP.J.1329.2024.03013

©《康复学报》编辑部,开放获取CC BY-NC-ND 4.0协议

© Rehabilitation Medicine, OA under the CC BY-NC-ND 4.0

究证实 tDCS 刺激 PSCI 患者脑部功能区会激起相应能力的恢复^[12]。通过查阅和整理相关文献,从 tDCS 治疗 PSCI 的角度出发,本文总结了 tDCS 治疗 PSCI 的机制、时机等相关研究进展,为 PSCI 后续的精准康复奠定基础。

1 卒中后认知障碍

PSCI 被定义为一种临床综合征,泛指在脑卒中事件后出现且持续到 6 个月时仍存在的认知功能的神经退行性病变^[13-14]。据资料统计,超过 60% 的脑卒中患者存在认知功能障碍。此外,它与脑卒中的高复发率和较低的 5 年生存率也密切相关^[15]。PSCI 最常见的问题是高级大脑功能(如注意力、语言、记忆、执行和视觉空间功能)的中断。其中,工作记忆在执行复杂行为时发挥着根本作用,负责大脑执行日常活动(如记忆、沟通、计划、阅读和写作)的复杂认知功能^[16-17]。PSCI 的类型与脑卒中病变的特征(如大小或关键区域)有关,病理改变似阿尔茨海默病(Alzheimer's disease, AD),其发病的血管性影响因素包括高血压病、高脂血症、糖尿病、吸烟等^[18]。PSCI 患者需要持续护理,增加了家庭护理人员的身心负担、社会的医疗和经济负担。对于青年患者而言,工作记忆的恢复和重返社会的能力举足轻重;对于老年患者而言,日常生活活动和整体康复同样不可或缺^[19-20]。PSCI 已成为一个必须立即解决的公共卫生问题^[21]。

2 tDCS 概述

tDCS 于 2000 年首次开发并应用于临床研究^[22],是一种很有前途的神经系统疾病调节技术,现已成为神经学科的一种常用治疗手段^[23]。治疗元件由阳极和阴极 2 个表面电极组成,放置于人体头部皮肤表层,阳极通过提高皮质兴奋性而诱导去极化,阴极通过降低皮质兴奋性而诱导超极化^[24]。与其他非侵入性脑刺激技术比较,tDCS 的临床应用具有更高的安全性,出现癫痫、躁狂等不良反应的现象极少。最常见的不良反应为治疗时电极片下有轻微麻刺感或痛感,通常在数小时内即可好转^[25]。由于 tDCS 仅引起与阈下刺激、空间分布率和聚焦度低等原因,它产生的实际效果有赖于电极片的大小、极性、位置、电流强度、刺激时间、部位、电导率、电阻等^[26]。BIKSON 等^[27]研究表明,作用效果的差异是由于:①解剖学特点(即电极如何放置和电流以何种方式到达大脑靶区);②活动选择性和任务特

异性(即在某一活动期间内,活跃的神经网络优先受到 tDCS 的刺激);③输入选择性(即 tDCS 将改变神经元系统的输入,从而增强信息处理)。KANG 等^[28]研究表明,阳极 tDCS 刺激显著改善了 PSCI 患者的注意功能。SMIRNI 等^[29]发现,右侧背外侧前额叶皮层(dorsolateral prefrontal cortex, DLPFC)的阴极 tDCS 可以改善健康人的识别记忆。SHAKER 等^[30]用双侧 tDCS 给 PSCI 患者治疗时,发现注意力和逻辑推理能力显著改善。SIA 等^[31]在 VR 训练中证实同侧 M1 区应用阳极 tDCS 对脑卒中患者的上肢功能、认知功能和执行功能是有效的。综上所述,tDCS 是一项潜能无限的无创性神经系统治疗手段。

3 tDCS 治疗卒中后认知障碍研究进展

3.1 tDCS 的参数

tDCS 以非侵入性脑刺激的形式,向头皮发送 1~2 mA 强度直流电,影响阈下神经元的兴奋性,调节受刺激区域的神经活动^[32]。为了达到通过颅骨传递到皮层脑区的治疗效果,通常需要连续作用 20~30 min^[33]。因不同的人具有不同的电导率、头皮电阻,治疗时仍需调选个体化的刺激参数。DLPFC 是目前普遍所知的认知功能的重要部位。有神经影像学支持,右侧和左侧 DLPFC 是认知功能相关区域,在大脑皮质中具有重要的联络作用^[34]。DLPFC 在选择性注意力、工作记忆和情景记忆中发挥作用^[35-36]。其中,工作记忆对应区域是大脑外侧前额叶和顶叶皮层的一部分^[37],由大脑中动脉和前动脉分支提供,随后排入大脑静脉窦,影响这些区域会损害其对应功能。有研究将左侧 DLPFC 作为研究的目标区域^[38]。多项试验数据表明,阳极 tDCS 刺激左侧 DLPFC 可以提升患者的学习能力,包括反应时间、工作记忆及语义的编码等^[39-42]。OHN 等^[43]研究发现给予左侧 DLPFC 的阳极 tDCS 可积极改善工作记忆。究其原因,考虑到大脑半球间兴奋性失衡理论:当一个半球的 DLPFC 损伤失去了异体抑制时,通过阳极或阴极应用 tDCS 刺激纠正,阳极刺激对受影响的半球产生兴奋性效果,阴极刺激对未受影响的大脑半球产生抑制性效果,从而恢复两个半球的平衡,恢复其功能^[44-45]。此外,DLPFC 并不是唯一有益的部位。WANG 等^[46]认为双侧 M1 区的治疗计划对改善脑卒中患者的记忆功能是有效的。ROY 等^[47]的研究报告中提到,在右顶叶皮层施加 1.5 mA 的阳极刺激已被证明可以调节空间注意力,然而刺激 DLPFC 上的树突状细胞并不能调节注意力。目

前尚不清楚 DLPFC 能否作为所有患者的有效刺激位置。与 tDCS 相比,高精度直流电刺激(high-definition transcranial direct current stimulation, HD-tDCS)具有更精确的皮质定位性和耐受性,能提供更好更持久的治疗效果。有研究者使用 HD-tDCS 刺激左侧 DLPFC、前额叶,结果显示工作记忆等认知能力有所提高^[48]。前岛叶也可作为 HD-tDCS 的刺激靶区,探究其对注意力控制、知觉处理、执行控制的改善效果^[49]。目前仍需进一步研究 HD-tDCS 刺激不同区域的效果,以准确掌握临床应用的可靠靶点。

3.2 tDCS的作用机制

3.2.1 tDCS对神经递质、神经元的影响 KENNEY-JUNG 等^[50]和 NITSCHKE 等^[51]发现,阳极 tDCS 刺激可以促进神经元的细胞膜去极化,增强 N-甲基-D 天冬氨酸 NMDA 受体功能并增加皮层兴奋性,阴极 tDCS 刺激可以促进神经元的细胞膜超极化并降低皮层兴奋性。据 MONAI 等^[52]和 ANTONENKO 等^[53]研究,tDCS 可以通过改变星形胶质细胞中钙离子和 γ -氨基丁酸的浓度来调节突触可塑性。此外,DI LAZARO 等^[54]研究发现 tDCS 诱导的后效应可能是 NMDA、GABA 以及多巴胺等的浓度变化。阳极刺激的长期效应可能是通过谷氨酸转移调制传递的。简而言之,tDCS 可以通过调节神经元的状态、神经递质的量、代谢物的浓度发挥作用,拥有较大的神经康复潜能。

3.2.2 tDCS对脑血流的影响 发生缺血性脑卒中时,大脑的对应功能区因失去血供而功能受损。BRAGINA 等^[55]发现阳极 tDCS 可以诱导小动脉扩张并调节毛细血管内的血流速度,引起脑血流量增加。NELSON 等^[56]通过测定 tDCS 治疗组的脑血流速度和血氧饱和度发现其结果明显高于空白对照组。研究也阐述了阳极 tDCS 促进 DLPFC 脑区的血流灌注、改善微循环的理论^[57]。因此,合理推断 tDCS 阳极刺激是通过扩张脑内血管,加快脑血流速度,从而减少脑梗死区域的损伤和再灌注损伤。

3.2.3 tDCS对大脑功能区域连接作用的影响 有学者推测运动皮质等大脑的某些功能区域存在功能连接。通过功能磁共振成像(functional magnetic resonance imaging, fMRI)验证 tDCS 会改变功能区域的功能连接性和关联区域脑白质的纤维连接性^[58]。tDCS 不仅可以解决 DLPFC 的病理连接,还可以解决远处大脑区域之间的其他病理连接,从而改善 PSCI 病人的认知功能^[59-60]。MEINZER 等^[61]阐述了 tDCS 通过诱导任务相关区域和神经网络的激活和连接

来提高行为性能的机制。TAO 等^[62]研究脑卒中后认知功能有所改善患者的 fMRI,结果发现大脑区域在静息状态下的功能连接较前加强。综上所述,tDCS 通过增强脑功能区域的连接改善认知功能。

4 tDCS的作用时机及其效果

4.1 单次 tDCS 产生的即刻效应和短暂后效应

单次 tDCS 产生的即刻效应是指其引起阈下刺激,改变神经元膜内外电位差,从而调节神经元兴奋性。同时,tDCS 的刺激具有后效应,产生较为持久的影响,已知的后效应持续时间是 1 h^[63]。这种持久的影响是由于 N-甲基-达司他酸受体的修饰或 GABA 激活影响皮层的突触变化^[64]。叶闾芬等^[65]进行了一项随机对照试验,结果提示在 tDCS 的后效应期内加强康复训练能有效改善脑卒中后手功能康复。艾一楠等^[66]分别在 tDCS 同时、刺激后 4 h 进行常规康复治疗,4 周后的结果显示在 tDCS 同时进行常规训练效果更佳。分析其原因是即刻效应状态可以促进患者更好地完成认知任务练习。总而言之,tDCS 不仅可产生即刻的促进效应,而且在刺激后约 1 h 仍存在有效的后效应。

4.2 重复性 tDCS 产生的长时程增强和长时程抑制

重复性 tDCS 会产生长时程增强(long-term potentiation, LTP)和长时程抑制(long-term depression, LTD)效应。LTP/LTD 是一种神经可塑性模型,通过再可塑性调节使突触处于一种更易改变的状态之中。LTP 指突触传递的持续增强,是学习和记忆的基础^[67]。当中枢神经进入到兴奋状态,突触可塑性的阈值发生动态变化,患者可以更好地完成学习任务。余果等^[68]研究表明 tDCS 最少能在 <1 h 内引起中枢神经类似的 LTP/LTD 样可塑性的变化。除此之外,阳极 tDCS 诱导神经元膜去极化时,持续刺激引起的持续去极化使细胞内的 Na^+ 和 K^+ 增加,浓度过高时会导致神经元饱和,并激活电压依赖性离子通道(尤其是 Na^+ 和 K^+ 通道),阻止行为表现的进一步改善。因此,在刺激时间较长的情况下,最初的促进作用可能会逆转为抑制作用。因此在临床应用 tDCS 时应把握好治疗时机才能事半功倍。

4.3 tDCS的疗效时长

DOCKERY 等^[69]阐述了 tDCS 提高健康人的规划能力的持续时间为 6~12 个月。艾一楠等^[66]研究结果显示 tDCS 对 PSCI 患者的刺激效果可以维持到治疗结束后 1 个月。同时,治疗效果受技术内部因素的影响,包括电流密度、参比电极位置、刺激持续

时间和刺激间隔。外部因素包括刺激的皮质区域、使用的任务和受试者特征。

5 tDCS与其他治疗方案的联合

目前,PSCI患者的康复治疗种类繁多,如乙酰胆碱酯酶抑制剂等药物治疗、认知训练、虚拟现实技术、计算机辅助认知训练、经颅磁刺激、针灸、脑机接口、音乐疗法^[70]。其中,认知训练应用最广泛,它通过刺激和增强患者的视觉、听觉和触觉等感觉,针对性地进行回顾训练、定向训练、感知训练、推理训练等,但疗效存在部分患者配合度低、恢复缓慢等问题^[71]。新时代兴起的技术如虚拟现实技术,将训练任务集成到模拟环境中(如家庭、体育训练设施),通过沉浸式的游戏体验创造出更加真实的感受,富有趣味性,然而它侧重于需要更多身体动员才能配合,改善PSCI患者整体认知功能的有效性仍不确定^[72-74]。中国传统的针灸疗法,应用在PSCI中有较高的有效性和安全性,原因可能与抑制NF- κ B-p53活化和氧化应激有关^[75-76]。

在治疗方案上,设立目标也是一种有效的促进方法,与患者及其家人公开讨论目标,积极鼓励,消除心理障碍,使患者能够积极参与事先的设定目标^[77]。同时,恢复效果与训练的频率、强度有关。被动运动对恢复影响小,主动运动更能有效恢复患者的独立性^[78]。因此,应早期积极地进行主动性的康复训练。

认知功能的各种传统治疗手段虽各有所长,但仍存在着药物不良反应、治疗时间长、恢复慢等问题^[79]。联合应用各种认知康复手段,以期弥补单独应用的局限与不足,达到联合更佳的治疗效果。目前仍需探索PSCI的不同康复手段的相对价值来完善康复决策。

6 总结

PSCI的负面影响亟待解决,近年来的诊疗手段日新月异,将tDCS应用于PSCI的康复研究备受业界人士的重视。tDCS通过影响神经递质、脑血流、大脑功能连接产生疗效,其简单、便捷、安全、痛感低等优点拥有广阔的应用前景。PSCI的tDCS治疗方案通常为1~2 mA的刺激强度作用于背外侧前额叶皮层20~30 min。tDCS联合其他训练手段如认知训练、虚拟现实技术、针灸等更有益的治疗效果,但是tDCS的特殊性在于其存在短暂后效应和长时程抑制效应,因此把握好联合作用的时机才能得到

最大的获益。目前tDCS在PSCI的临床应用上仍然存在公认有效的方案不统一、介入时机不确定、合理的刺激时长不精确、对注意力和执行力等具体认知功能的目标脑区仍需精准定位等难题。同时,脑卒中后康复治疗的效果,根据脑卒中的类型、神经损伤的程度、个体的功能损伤程度、训练的频率和强度的不同,存在很大的异质性。此项难题的攻克将会大大减轻家庭和社会的重担。今后的PSCI康复方案应向联合优势互补的方向迈进,实现个体化的有效康复。

参考文献

- [1] FEIGIN V L, BRAININ M, NORRVING B, et al. World stroke organization (WSO): global stroke fact sheet 2022 [J]. *Int J Stroke*, 2022, 17(1): 18-29.
- [2] BOLOGNINI N, RUSSO C, SOUZA CARNEIRO M I, et al. Bi-hemispheric transcranial direct current stimulation for upper-limb hemiparesis in acute stroke: a randomized, double-blind, sham-controlled trial [J]. *Eur J Neurol*, 2020, 27(12): 2473-2482.
- [3] GEED S, FEIT P, EDWARDS D F, et al. Why are stroke rehabilitation trial recruitment rates in single digits? [J]. *Front Neurol*, 2021, 12: 674237.
- [4] KIM C H, CHU H M, KANG G H, et al. Difference in gait recovery rate of hemiparetic stroke patients according to paralyzed side: a cross-sectional study based on a retrospective chart review [J]. *Medicine*, 2019, 98(46): 18023.
- [5] LABBERTON A S, BARRA M, RØNNING O M, et al. Patient and service factors associated with referral and admission to inpatient rehabilitation after the acute phase of stroke in Australia and Norway [J]. *BMC Health Serv Res*, 2019, 19(1): 871.
- [6] TOYODA K, YOSHIMURA S, NAKAI M, et al. Twenty-year change in severity and outcome of ischemic and hemorrhagic strokes [J]. *JAMA Neurol*, 2022, 79(1): 61-69.
- [7] PENDLEBURY S T, ROTHWELL P M, OXFORD VASCULAR STUDY. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study [J]. *Lancet Neurol*, 2019, 18(3): 248-258.
- [8] FRIDE Y, ADAMIT T, MAEIR A, et al. What are the correlates of cognition and participation to return to work after first ever mild stroke? [J]. *Top Stroke Rehabil*, 2015, 22(5): 317-325.
- [9] OKSALA N K, JOKINEN H, MELKAS S, et al. Cognitive impairment predicts poststroke death in long-term follow-up [J]. *J Neurol Neurosurg Psychiatry*, 2009, 80(11): 1230-1235.
- [10] BOSMA M S, NIJBOER T C W, CALJOUW M A A, et al. Impact of visuospatial neglect post-stroke on daily activities, participation and informal caregiver burden: a systematic review [J]. *Ann Phys Rehabil Med*, 2020, 63(4): 344-358.
- [11] ZHANG J, SONG S H, ZHAO Y, et al. Economic burden of comorbid chronic conditions among survivors of stroke in China: 10-year longitudinal study [J]. *BMC Health Serv Res*, 2021,

- 21(1):978.
- [12] 曲斯伟,宋为群. 经颅直流电刺激在卒中后认知功能障碍康复中的研究进展[J]. 中国脑血管病杂志,2016,13(4):219-224.
QU S W, SONG W Q. Research progress of transcranial direct current stimulation in rehabilitation of cognitive dysfunction after stroke [J]. *Chin J Cerebrovasc Dis*, 2016, 13(4): 219-224.
- [13] 汪凯,董强,郁金泰,等. 卒中后认知障碍管理专家共识2021[J]. 中国卒中杂志,2021,16(4):376-389.
WANG K, DONG Q, YU J T, et al. Experts consensus on post-stroke cognitive impairment management 2021 [J]. *Chin J Stroke*, 2021, 16(4): 376-389.
- [14] VERDELHO A, WARDLAW J, PAVLOVIC A, et al. Cognitive impairment in patients with cerebrovascular disease: a white paper from the links between stroke ESO Dementia Committee [J]. *Eur Stroke J*, 2021, 6(1): 5-17.
- [15] LINDELØV J K, OVERGAARD R, OVERGAARD M. Improving working memory performance in brain-injured patients using hypnotic suggestion [J]. *Brain*, 2017, 140(4): 1100-1106.
- [16] XU J J, REN M, ZHAO J J, et al. Effectiveness of theta and gamma electroacupuncture for post-stroke patients on working memory and electrophysiology: study protocol for a double-center, randomized, patient- and assessor-blinded, sham-controlled, parallel, clinical trial [J]. *Trials*, 2020, 21(1): 910.
- [17] MOK V C, LAM B Y, WONG A, et al. Early-onset and delayed-onset poststroke dementia-revisiting the mechanisms [J]. *Nat Rev Neurol*, 2017, 13(3): 148-159.
- [18] RIMMELE D L, THOMALLA G. Long-term consequences of stroke [J]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*, 2022, 65(4): 498-502.
- [19] LEVINE D A, GALECKI A T, LANGA K M, et al. Trajectory of cognitive decline after incident stroke [J]. *JAMA*, 2015, 314(1): 41-51.
- [20] ROCHMAH T N, RAHMAWATI I T, DAHLUI M, et al. Economic burden of stroke disease: a systematic review [J]. *Int J Environ Res Public Health*, 2021, 18(14): 7552.
- [21] NITSCHKE M A, PAULUS W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation [J]. *J Physiol*, 2000, 527(Pt 3): 633-639.
- [22] LEFAUCHEUR J P, ANTAL A, AYACHE S S, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS) [J]. *Clin Neurophysiol*, 2017, 128(1): 56-92.
- [23] TEGELER C L, GERDES L, SHALTOUT H A, et al. Successful use of closed-loop allostatic neurotechnology for post-traumatic stress symptoms in military personnel: self-reported and autonomic improvements [J]. *Mil Med Res*, 2017, 4(1): 38.
- [24] LIEBETANZ D, NITSCHKE M A, TERGAU F, et al. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability [J]. *Brain*, 2002, 125(Pt 10): 2238-2247.
- [25] 中国经颅直流电刺激脑卒中康复临床应用专家共识组. 经颅直流电刺激技术应用于脑卒中患者康复治疗专家共识[J]. 中华物理医学与康复杂志, 2021, 43(4): 289-294.
Expert consensus group on clinical application of transcranial direct current stimulation in stroke rehabilitation in China. Expert consensus on the application of transcranial direct current stimulation technology in rehabilitation treatment of stroke patients [J]. *Chin J Phys Med Rehabil*, 2021, 43(4): 289-294.
- [26] MEDEIROS L F, DE SOUZA I C C, VIDOR L P, et al. Neurobiological effects of transcranial direct current stimulation: a review [J]. *Front Psychiatry*, 2012, 3: 110.
- [27] BIKSON M, NAME A, RAHMAN A. Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms [J]. *Front Hum Neurosci*, 2013, 7: 688.
- [28] KANG E K, BAEK M J, KIM S, et al. Non-invasive cortical stimulation improves post-stroke attention decline [J]. *Restor Neurol Neurosci*, 2009, 27(6): 645-650.
- [29] SMIRNI D, TURRIZIANI P, MANGANO G R, et al. Modulating memory performance in healthy subjects with transcranial direct current stimulation over the right dorsolateral prefrontal cortex [J]. *PLoS One*, 2015, 10(12): e0144838.
- [30] SHAKER H A, SAWAN S A E, FAHMY E M, et al. Effect of transcranial direct current stimulation on cognitive function in stroke patients [J]. *Egypt J Neurol Psychiatr Neurosurg*, 2018, 54(1): 32.
- [31] LEE S A, CHA H. The effect of clinical application of transcranial direct current stimulation combined with non-immersive virtual reality rehabilitation in stroke patients [J]. *Technol Health Care*, 2022, 30(1): 117-127.
- [32] NITSCHKE M A, PAULUS W. Transcranial direct current stimulation: update 2011 [J]. *Restor Neurol Neurosci*, 2011, 29(6): 463-492.
- [33] KUO M F, NITSCHKE M A. Effects of transcranial electrical stimulation on cognition [J]. *Clin EEG Neurosci*, 2012, 43(3): 192-199.
- [34] NEJATI V, SALEHINEJAD M A, NITSCHKE M A, et al. Transcranial direct current stimulation improves executive dysfunctions in ADHD: implications for inhibitory control, interference control, working memory, and cognitive flexibility [J]. *J Atten Disord*, 2020, 24(13): 1928-1943.
- [35] TSAI P Y, LIN W S, TSAI K T, et al. High-frequency versus theta burst transcranial magnetic stimulation for the treatment of post-stroke cognitive impairment in humans [J]. *J Psychiatry Neurosci*, 2020, 45(4): 262-270.
- [36] BRESSLER S L, MENON V. Large-scale brain networks in cognition: emerging methods and principles [J]. *Trends Cogn Sci*, 2010, 14(6): 277-290.
- [37] NORD C L, POPA T, SMITH E, et al. The effect of frontoparietal paired associative stimulation on decision-making and working memory [J]. *Cortex*, 2019, 117: 266-276.
- [38] MANSOURI F, MIR-MOGHTADAEI A, NIRANJAN V, et al. Development and validation of a 3D-printed neuronavigation headset for therapeutic brain stimulation [J]. *J Neural Eng*, 2018, 15(4): 046034.
- [39] DEDONCKER J, BRUNONI A R, BAEKEN C, et al. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation pa-

- rameters [J]. *Brain Stimul*, 2016, 9(4): 501–517.
- [40] BRUNONI A R, VANDERHASSELT M A. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis [J]. *Brain Cogn*, 2014, 86: 1–9.
- [41] KIM K, EKSTROM A D, TANDON N. A network approach for modulating memory processes via direct and indirect brain stimulation: toward a causal approach for the neural basis of memory [J]. *Neurobiol Learn Mem*, 2016, 134(Pt A): 162–177.
- [42] HILL A T, ROGASCH N C, FITZGERALD P B, et al. Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults [J]. *NeuroImage*, 2017, 152: 142–157.
- [43] OHN S H, PARK C I, YOO W K, et al. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory [J]. *Neuroreport*, 2008, 19(1): 43–47.
- [44] MADHAVAN S, SHAH B. Enhancing motor skill learning with transcranial direct current stimulation—concise review with applications to stroke [J]. *Front Psychiatry*, 2012, 3: 66.
- [45] DUBOVIK S, PTAK R, ABOULAFIA T, et al. EEG alpha band synchrony predicts cognitive and motor performance in patients with ischemic stroke [J]. *Behav Neurol*, 2013, 26(3): 187–189.
- [46] WANG Y, LIU W, CHEN J, et al. Comparative efficacy of different noninvasive brain stimulation therapies for recovery of global cognitive function, attention, memory, and executive function after stroke: a network meta-analysis of randomized controlled trials [J]. *Ther Adv Chronic Dis*, 2023, 14: 20406223231168754.
- [47] ROY L B, SPARING R, FINK G R, et al. Modulation of attention functions by anodal tDCS on right PPC [J]. *Neuropsychologia*, 2015, 74: 96–107.
- [48] VERGALLITO A, VAROLI E, PISONI A, et al. State-dependent effectiveness of cathodal transcranial direct current stimulation on cortical excitability [J]. *Neuroimage*, 2023, 277: 120242.
- [49] MOLNAR-SZAKACS I, UDDIN L Q. Anterior insula as a gatekeeper of executive control [J]. *Neurosci Biobehav Rev*, 2022, 139: 104736.
- [50] KENNEY-JUNG D L, BLACKER C J, CAMSARI D D, et al. Transcranial direct current stimulation: mechanisms and psychiatric applications [J]. *Child Adolesc Psychiatr Clin N Am*, 2019, 28(1): 53–60.
- [51] NITSCHKE M A, FRICKE K, HENSCHKE U, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans [J]. *J Physiol*, 2003, 553(Pt 1): 293–301.
- [52] MONAI H, OHKURA M, TANAKA M, et al. Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain [J]. *Nat Commun*, 2016, 7: 11100.
- [53] ANTONENKO D, SCHUBERT F, BOHM F, et al. tDCS-induced modulation of GABA levels and resting-state functional connectivity in older adults [J]. *J Neurosci*, 2017, 37(15): 4065–4073.
- [54] DI LAZZARO V, MANGANELLI F, DILEONE M, et al. The effects of prolonged cathodal direct current stimulation on the excitatory and inhibitory circuits of the ipsilateral and contralateral motor cortex [J]. *J Neural Transm*, 2012, 119(12): 1499–1506.
- [55] BRAGINA O A, LARA D A, NEMOTO E M, et al. Increases in microvascular perfusion and tissue oxygenation via vasodilatation after anodal transcranial direct current stimulation in the healthy and traumatized mouse brain [J]. *Adv Exp Med Biol*, 2018, 1072: 27–31.
- [56] NELSON J T, MCKINLEY R A, GOLOB E J, et al. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS) [J]. *Neuroimage*, 2014, 85 (Pt 3): 909–917.
- [57] STAGG C J, LIN R L, MEZUE M, et al. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex [J]. *J Neurosci*, 2013, 33(28): 11425–11431.
- [58] LOWE M J, MOCK B J, SORENSON J A. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations [J]. *NeuroImage*, 1998, 7(2): 119–132.
- [59] CHENG C P W, WONG C S M, LEE K K, et al. Effects of repetitive transcranial magnetic stimulation on improvement of cognition in elderly patients with cognitive impairment: a systematic review and meta-analysis [J]. *Int J Geriatr Psychiatry*, 2018, 33(1): 1–13.
- [60] GREFKES C, FINK G R. Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches [J]. *Brain*, 2011, 134(Pt 5): 1264–1276.
- [61] MEINZER M, LINDENBERG R, ANTONENKO D, et al. Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes [J]. *J Neurosci*, 2013, 33(30): 12470–12478.
- [62] LIN Z C, TAO J, GAO Y L, et al. Analysis of central mechanism of cognitive training on cognitive impairment after stroke: resting-state functional magnetic resonance imaging study [J]. *J Int Med Res*, 2014, 42(3): 659–668.
- [63] JOHANSSON B B. Current trends in stroke rehabilitation. A review with focus on brain plasticity [J]. *Acta Neurol Scand*, 2011, 123(3): 147–159.
- [64] STAGG C J, BEST J G, STEPHENSON M C, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation [J]. *J Neurosci*, 2009, 29(16): 5202–5206.
- [65] 叶茵芬, 余齐卫, 刘毅, 等. tDCS后效应对卒中后手功能康复疗效的临床研究[J]. *中国康复*, 2018, 33(4): 289–292.
- YE T F, YU Q W, LIU Y, et al. Clinical study on the post-effect of tDCS on the rehabilitation of hand function after stroke [J]. *Chin J Rehabil*, 2018, 33(4): 289–292.
- [66] 艾一楠, 李莉莉, 尹明宇, 等. 不同治疗时机的经颅直流电刺激治疗脑卒中后认知障碍的初步研究[J]. *中国康复医学杂志*, 2021, 36(3): 315–321.
- AI Y N, LI L L, YIN M Y, et al. Preliminary study on the treatment of cognitive impairment after stroke by transcranial direct current stimulation at different treatment opportunities [J]. *Chin J Rehabil Med*, 2021, 36(3): 315–321.
- [67] ANDREWS S C, HOY K E, ENTICOTT P G, et al. Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorso-

- lateral prefrontal cortex [J]. *Brain Stimul*, 2011, 4(2):84-89.
- [68] 余果, 孙倩倩, 肖阳, 等. tDCS 预刺激增强脑卒中认知功能障碍患者认知康复疗效的临床研究[J]. *中国康复*, 2020, 35(3): 131-134.
- YU G, SUN Q Q, XIAO Y, et al. Clinical study on the effect of tDCS pre-stimulation on cognitive rehabilitation of stroke patients with cognitive impairment [J]. *Chin J Rehabil*, 2020, 35(3): 131-134.
- [69] DOCKERY C A, HUECKEL W R, BIRBAUMER N, et al. Enhancement of planning ability by transcranial direct current stimulation [J]. *Neurosci*, 2009, 29(22):7271-7277.
- [70] SU K Q, YUAN J, LIU H H, et al. The comparative effectiveness of traditional Chinese medicine exercise therapies in elderly people with mild cognitive impairment: a systematic review and network meta-analysis [J]. *Front Neurol*, 2022, 13:775190.
- [71] CHUNG C S, POLLOCK A, CAMPBELL T, et al. Cognitive rehabilitation for executive dysfunction in adults with stroke or other adult non-progressive acquired brain damage [J]. *Cochrane Database Syst Rev*, 2013, 2013(4):CD008391.
- [72] CHATTERJEE K, BUCHANAN A, COTTRELL K, et al. Immersive virtual reality for the cognitive rehabilitation of stroke survivors [J]. *IEEE Trans Neural Syst Rehabil Eng*, 2022, 30:719-728.
- [73] QIAN J L, MCDONOUGH D J, GAO Z. The effectiveness of virtual reality exercise on individual's physiological, psychological and rehabilitative outcomes: a systematic review [J]. *Int J Environ Res Public Health*, 2020, 17(11):4133.
- [74] ZHANG Q, FU Y, LU Y H, et al. Impact of virtual reality-based therapies on cognition and mental health of stroke patients: systematic review and meta-analysis [J]. *J Med Internet Res*, 2021, 23(11):31007.
- [75] KUANG X, FAN W J, HU J W, et al. Acupuncture for post-stroke cognitive impairment: a systematic review and meta-analysis [J]. *Acupunct Med*, 2021, 39(6):577-588.
- [76] YANG J W, WANG X R, MA S M, et al. Acupuncture attenuates cognitive impairment, oxidative stress and NF- κ B activation in cerebral multi-infarct rats [J]. *Acupunct Med*, 2019, 37(5): 283-291.
- [77] PLANT S E, TYSON S F, KIRK S, et al. What are the barriers and facilitators to goal-setting during rehabilitation for stroke and other acquired brain injuries? A systematic review and meta-synthesis [J]. *Clin Rehabil*, 2016, 30(9):921-930.
- [78] HARRIS J E, ENG J J. Paretic upper-limb strength best explains arm activity in people with stroke [J]. *Phys Ther*, 2007, 87(1): 88-97.
- [79] URBANOVA B S, SCHWABOVA J P, MAGEROVA H, et al. Reduced cerebrovascular reserve capacity as a biomarker of microangiopathy in Alzheimer's disease and mild cognitive impairment [J]. *J Alzheimers Dis*, 2018, 63(2):465-477.

Research Progress of Transcranial Direct Current Stimulation Therapy for Cognitive Impairment after Stroke

LIU Yuanchen, ZHANG Lixin*

Shengjing Hospital of China Medical University, Shenyang, Liaoning 110000, China

*Correspondence: ZHANG Lixin, E-mail: zhanglx@sj-hospital.org

ABSTRACT Post-stroke cognitive impairment (PSCI) refers to the symptoms of cognitive decline after stroke, which seriously impairs patients' quality of life and survival time. Compared with cognitive impairment caused by other neurological diseases, preventability and treatability are important characteristics of PSCI, making early intervention particularly important. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique with the advantages of high safety and low pain, and it is an effective neurological rehabilitation treatment for PSCI. The tDCS treatment regimen for PSCI usually consists of a stimulation intensity of 1 to 2 mA applied to the dorsolateral prefrontal cortex for 20 to 30 minutes. The stimulation site is usually the dorsolateral prefrontal lobe, but researchers have also confirmed the effectiveness of other stimulation sites, such as the bilateral M1 area and right parietal cortex. tDCS improves cognitive function by affecting neurotransmitters (such as calcium ions and γ -aminobutyric acid in astrocytes), the state of neurons, cerebral blood flow, and the connectivity of functional areas of the brain. tDCS not only produces an immediate boosting effect and an after-effect that is effective about 1 hour after stimulation, but also has long-term enhancement (LTP) and long-term depression (LTD) effects. Therefore, the timing of treatment should be grasped when tDCS is applied clinically. At present, various traditional treatments for cognitive function (such as drug therapy, cognitive training, virtual reality technology, acupuncture, etc.) have their own strengths, but there are still problems such as adverse drug reactions, long treatment time and slow recovery. In order to overcome the limitations and shortcomings of tDCS alone and to achieve a better therapeutic effect, the combined application of other cognitive rehabilitation measures at the same time or within 1 hour of tDCS stimulation is an alternative approach. This article aims to review the research progress of tDCS and other cognitive rehabilitation methods in PSCI, so as to provide therapeutic experience and reference for the comprehensive rehabilitation of PSCI.

KEY WORDS post-stroke cognitive impairment; stroke; transcranial direct current stimulation; combination therapy; timing

DOI:10.3724/SP.J.1329.2024.03013