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· 专题 ·

经颅直流电刺激对老化和阿尔茨海默病认知功能影响的研究进展

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摘要

老化导致认知功能下降, 包括记忆、注意、语言和执行等功能。阿尔茨海默病(AD)是一种与年龄密切相关的进行性神经退行性疾病, 认知功能下降是其核心症状之一。经颅直流电刺激(tDCS)已被应用于健康老年人和 AD 患者, 改善生理和病理性老化相关的认知障碍。tDCS 能改善老年人的记忆(情景记忆、语义记忆和工作记忆)、语言、错误感知和注意功能, 其效果受教育水平、刺激参数和个人任务基线成绩等多种因素影响。tDCS 也能改善 AD 患者的认知功能, 效果受解剖差异、疾病严重程度、刺激参数以及评估工具等因素影响。认知训练与 tDCS 结合可进一步增强老年人和 AD 患者认知功能。

关键词 老化; 阿尔茨海默病; 经颅直流电刺激; 认知功能; 综述

Effects of Transcranial Direct Current Stimulation on Cognitive Function after Aging and Alzheimer's Disease (review)

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Abstract

Aging leads to cognitive decline, including memory, attention, language and execution. Alzheimer's disease (AD) is a progressive neurodegenerative disorder closely related to age. Decreased cognitive function is one of its core symptoms. Transcranial direct current stimulation (tDCS) has been used in old healthy adults and AD patients to improve aging-related cognitive impairment. tDCS can improve memory (situational memory, semantic memory and working memory), language, error awareness and attentional functions in the old adults, which were influenced by many factors, such as education levels, stimulation parameters and individual task baseline scores, etc. For AD patients, tDCS may improve their cognitive function, which is influenced by the factors as anatomical differences, severity of disease, stimulation parameters and assessment tools, etc. Cognitive training combined with tDCS can further improve cognitive function in old adults and AD patients.

Key words: aging; Alzheimer's disease; transcranial direct current stimulation; cognitive function; review

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老化导致认知功能下降, 包括注意力、记忆力、语言和执行功能^[1]。这些年龄相关的认知缺陷对老年人的日常生活活动和生活质量产生深远的影响^[2]。随着预期寿命逐渐增加^[3], 延缓与年龄相关认知下降的策略越来越受到关注。

阿尔茨海默病(Alzheimer's disease, AD)是一种进展性神经退行性疾病, 核心症状为日常生活能力降低、精神行为异常和认知功能下降(记忆、语言和执行功能等)。随着年龄增长, AD发病率急剧增加, 阿尔茨海默病协会最新报告指出^[4], 仅在美国, 2018年, 65~74岁人群中约有66 000例新病例, 75~84岁人群中约有173 000例新病例, 85岁及以上人群中新增病例245 000例。这意味着65~74岁人群每1000人约有2个新病例, 75~84岁人群中每1000人新增11个病例, 而85岁及以上人群中每1000人有37个新病例。迄今为止, 胆碱酯酶抑制剂和谷氨酸受体阻滞剂是AD患者的主要治疗方法。然而药物治疗效果有限, 并有不良反应^[5]。开发替代疗法有重要意义。

近几年, 经颅直流电刺激(transcranial direct current stimulation, tDCS)已被应用于健康老年人和AD患者, 通过促进大脑可塑性, 改善生理和病理性老化相关认知障碍^[6]。tDCS是一种非侵入性神经调节技术, 通过两个或多个电极, 在头皮释放微弱直流电(1~2 mA), 调节神经细胞跨膜电位。阴极刺激通过神经元超极化降低皮质兴奋性, 而阳极刺激通过阈下刺激神经元去极化, 增加皮质兴奋性^[7]。tDCS的作用机制尚不完全清楚, 可能与神经回路中长时间增强(long-term potentiation, LTP)和长时间抑制(long-term depression, LTD)有关^[8]。LTP/LTD效应是大脑可塑性的关键机制, 尤其在学习和记忆方面。

tDCS的效果主要取决于刺激参数, 包括极性、电极片面积大小、刺激周期和电流强度等。其他一些因素也可能影响电流分布, 从而影响tDCS疗效, 包括头颅解剖结构(颅骨厚度、灰质和白质密度以及脑脊液体积)和脑损伤情况。tDCS刺激强度在运动和认知领域有非线性依赖效应^[9-10], 较高的电流并不意味着效果更好。

1 老化

随着大脑生理性老化, 认知功能逐渐下降。一项综述认为^[11], 尽管在认知领域, 方案设计和结果方面存在差异, 但总体表明, 经颅磁刺激(transcranial magnetic stimulation, TMS)和tDCS可增强健康老年人的认知功能, 大多数研究认为tDCS特别适合于提高认知能力, 包括记忆、语言、错误感知和注意等方面。

1.1 记忆

在tDCS调节认知功能方面, 研究最多的是记忆, 尤其是情景记忆(个人在特定时间、地点经历的事情和经验的记忆), 常选用阳极刺激。

1.1.1 单独应用tDCS

Flöel等^[12]利用阳极tDCS(1 mA, 20 min)刺激老年人右侧颞顶叶皮层(temporoparietal cortex, TPC), Sandrini等^[13]利用阳极tDCS(1.5 mA, 15 min)刺激老年人左侧前额叶皮层(prefrontal cortex, PFC), Sandrini等^[14]利用阳极tDCS(1.5 mA, 15 min)刺激老年人左侧或右侧前额叶皮质背外侧(dorsolateral prefrontal cortex, DLPFC), 均发现情景记忆改善。Manenti等^[15]用tDCS(1.5 mA)刺激老年人左侧或右侧DLPFC以及顶叶皮层(parietal cortex, PARC), 发现只有刺激左侧DLPFC或PARC时才能改善情景记忆, 提示与年龄相关的加工过程偏侧化。Ross等^[16]在左侧或右侧前额叶(anterior temporal lobe, ATL)施加tDCS(1.5 mA, 15 min), 也发现只有刺激左侧区域才能改善语义记忆。

工作记忆是指在短时间内编码、存储、保持和操作信息的系列认知过程。随着年龄的增长, 工作记忆效率下降^[17-18], 与大脑活动和连接模式改变(老年人有更多双侧额叶活动)有关^[19]。在左侧、右侧DLPFC施以阳极tDCS(1.5 mA, 10 min), 接受过更多教育的老年人工作记忆表现改善, 但在受教育程度较低的老年人中未发现改善, 提示tDCS的作用效果与教育水平有关^[20]。

tDCS改善老年人记忆功能的脑网络机制, 主要与PFC及默认模式网络(default mode network, DMN)有关。在执行特定认知任务期间, 老年人PFC不对称性减少, 双侧激活增多^[21]; 神经元活动从后部转到前部, 即更有可能激活PFC而不是枕-颞叶皮层^[22]。DMN随年龄增加而显著改变^[23]。老年人后扣带回DMN活性显著降低, 且其他DMN区域活性较低^[24], 功能连接也有所减少^[25]。阳极tDCS刺激老年人左额下回, 利用静息态功能磁共振(resting-state fMRI, rs-fMRI)评估脑网络变化, 与年轻人相比, 假刺激期间, 老年人双侧PFC活动增加与任务表现降低有关; 阳极tDCS显著改善老年人表现, 达到年轻人的水平, 显著降低双侧PFC、前扣带回和楔前叶中与任务相关的活动过度^[26]。

事件相关电位常用于研究tDCS对认知功能的调节机制, 在工作记忆研究方面常选用P300。P300潜伏期与上下文信息更新速度有关, 其中顶叶P300的振幅与分配给上下文信息更新过程的神经活动量有关, 而额叶P300的振幅与分配给即将到来的刺激的注意资源有关^[27]。研究发现^[28], P300潜伏期延迟及振幅降低与衰老有关, 这被解释为额叶补偿与年龄相关的认知功能下降。左侧DLPFC阳极tDCS可改善老年人工作记忆, 可能与促进额叶补偿机制有关^[29]。

1.1.2 联合认知训练

认知训练通过反复激活与认知任务相关的特定神经环路来增强神经网络^[30]。认知训练对老年人的记忆增益远小于年轻

人^[31]。此外,认知训练通常很耗时,随着时间的推移,训练的动机和依从性降低^[32]。认知训练与 tDCS 相结合,可以进一步提高训练效果^[33-34]。

在健康成年人中,阳极 tDCS 联合计算机认知训练可增强认知训练效果^[35]。研究发现^[36],对 40 例 65 岁健康老年人行双侧 PFC 阳极 tDCS 联合计算机辅助认知训练,相比假刺激组,能显著改善言语工作记忆任务和数字跨度测试的准确性,且改善言语工作记忆的效果可持续至少 4 周。

物体位置记忆对于适应日常生活中不断变化的环境至关重要,但会随着老化而下降,在轻度认知障碍(mild cognitive impairment, MCI)等病理状态下加速下降,而且可能是神经退行性疾病的初期标志^[37]。Antonenko 等^[38]发现,阳极 tDCS 可增强物体位置记忆训练效果,这与默认网络的改变有关。但另一项假刺激盲交叉研究得出不一样的结果^[39],原因可能是研究测试形式和时间不同,另外 tDCS 是一种相对较弱的调节形式^[40],显著的认知训练收益可能掩盖了阳极 tDCS 的轻微作用^[41]。需要更多研究验证 tDCS 联合认知训练对老年人记忆的效果。

1.2 语言功能

在语言领域, tDCS 研究多关注老年人的命名功能。Fertonani 等^[42]用左侧 DLPFC 阳极 tDCS (2 mA)干预,发现只有在任务执行期间(在线 tDCS)应用,才对健康老年人的命名能力有益。基于运动系统预激活可改善语言加工过程的理论,Meinzer 等^[43]在老年人执行语义词汇检索及运动言语任务时,采用 tDCS (1 mA, 30 min)刺激老年人左侧或右侧初级运动皮层(M1),结果发现阳极 tDCS 刺激 M1 可显著改善词汇检索; fMRI 显示,在运动言语任务期间的神经易化可降低用于词汇检索和言语加工的交叉神经系统之间的转换成本,从而改善任务成绩。

1.3 错误感知

Harty 等^[44]采用右侧 DLPFC tDCS (1 mA)治疗健康老年人错误感知,刺激持续时间取决于错误意识的计算机化测试任务的长度,与假刺激和阴极刺激相比,阳极 tDCS 显著降低错误感知。

1.4 注意

Learmonth 等^[45]在单侧视觉滴定检测任务期间,对健康年轻人和老年人采用右侧和左侧后顶叶皮质阳极 tDCS (1 mA, 15 min),发现效果与年龄无关,而与个人任务基线成绩有关。

总的来说, tDCS 有助于改善健康老年人认知功能。由于认知功能的多样性和复杂性,需要更多研究验证对具体认知功能的作用。

2 AD

在 AD 中, A β 沉积和 tau 蛋白过度磷酸化引起突触功能障碍、神经回路异常和脑网络受损,导致各种认知及行为症状。tDCS 通过调节神经元静息电位、突触可塑性、皮层神经递质、星形胶质细胞、脑血流量和功能连接性,改善认知功能^[46-48],被认为是 AD 的替代疗法。虽然目前 tDCS 治疗 AD 的研究数量

较少,但前景广阔。

AD 患者早期主要表现为记忆障碍,其中情景记忆是 AD 患者最早下降的认知功能,因此针对 AD 的 tDCS 研究多集中于记忆方面。MRI 示大脑萎缩,以内侧颞叶及内嗅皮质最严重,是 AD 最早、最敏感的指征^[49]。由于颞叶与情景记忆密切相关且对记忆的巩固起重要作用, DLPFC 对记忆编码、工作记忆及执行控制功能起重要作用^[50]。因此 tDCS 刺激区域多选择颞叶和 DLPFC。

MCI 患者是转化为 AD 的高危人群。一项针对健康人群和 MCI 人群的 M1 阳极 tDCS 研究显示^[51], MCI 患者产生正确语义词检索反应比健康对照少,与双侧 PFC 活动过度有关;阳极 tDCS 显著降低与任务相关的 PFC 活动过度, rs-fMRI 显示网状结构“正常化”,从而改善 MCI 患者认知功能。另一项研究对 MCI 患者行左腹侧额下回阳极 tDCS (1 mA, 20 min), fMRI 显示脑功能连接正常化,患者认知功能改善^[52]。近期一项系统评价探讨 TMS 和 tDCS 在痴呆中的应用^[53],其中多数被试为 AD 患者(13 项研究)和 MCI 患者(4 项研究),尽管方案设计和结果存在差异,但总体表明 TMS 和 tDCS 可增强痴呆患者的认知功能。

2.1 单独应用 tDCS

Boggio 等^[54]对 10 例 AD 患者施加左侧 DLPFC 阳极 tDCS (2 mA, 30 min),患者视觉再认记忆改善;长期疗效观察发现^[55],双侧颞叶重复阳极 tDCS (2 mA, 30 min) 5 d,可提高 AD 患者的视觉再认记忆,效应持续至少 4 周。另一项研究对 10 例可能的 AD 患者行颞叶阳极 tDCS (1.5 mA, 15 min)^[56],其词语再认记忆改善。Khedr 等^[57]对 34 例 AD 患者行左侧 DLPFC 随机双盲假刺激对照试验(2 mA, 25 min, 持续 2 周共 10 次),结果显示,阳极 tDCS 能改善认知功能,后续效应长达 2 个月。1 例早发性 AD 患者每天接受 tDCS,共 8 个月,认知功能显著改善^[58]。但也有一项研究表明^[59],与假刺激相比,左颞叶阳极 tDCS (2 mA, 30 min, 6 次)未显著改善 AD 患者的言语记忆功能。研究者认为,原因可能包括患者解剖差异(如皮层厚度)、疾病严重程度(该研究的患者记忆障碍程度较重)、刺激参数不同以及评估工具不同。近期一项综述显示^[60],在纳入的 12 项研究中,10 项显示 tDCS 改善认知,影响因素包括刺激参数的异质性以及患者个体差异。

听觉诱发电位 P300 反映注意和记忆的加工过程,是 AD 的客观标记^[61],在 AD 患者中 P300 潜伏期延长^[62]。阳极 tDCS 缩短 P300 潜伏期^[57]。

总之,多数研究表明, tDCS 能改善 AD 患者认知功能,但效果受到多种因素(患者解剖差异、疾病严重程度、刺激参数不同以及评估工具)影响,尚需更多标准化研究验证 tDCS 效果。

2.2 联合认知训练

晚期 AD 患者仍保留部分认知功能,并有一定程度的功能可塑性,可通过认知训练维持甚至增强患者的认知功能,但需

要几周甚至几个月才能见效且作用有限^[32]。tDCS可改变突触可塑性,改善AD患者认知功能,两者结合可增强认知训练疗效^[63],是临床治疗AD的新趋势。

主观记忆主诉(subjective memory complaints, SMC)是指自我报告记忆力下降,但客观记忆表现在正常范围内,是AD相关MCI诊断标准之一,也是AD的独立风险因素^[64]。一项针对老年SMC患者研究发现^[65],在上下文提醒训练后实施左侧PFC阳极tDCS(1.5 mA),可改善记忆,效应持续30 d。额叶阳极tDCS(2 mA, 20 min)结合认知训练,能更有效地改善MCI患者脑功能连接及学习记忆功能^[66]。

一例60岁轻度AD男性患者接受DLPFC阳极tDCS(2 mA, 20 min, 持续2周,共10次)联合认知训练,认知成绩未见明显改善,但认知下降速度减慢,患者认知功能维持近3个月^[67]。这与Martin等^[65]的研究结果相似,tDCS有增强认知训练的长期效果。一项双盲交叉研究发现^[68],痴呆患者(AD或额颞叶痴呆)在图片命名训练期间应用顶下叶阳极tDCS(2 mA, 30 min, 10次)在线刺激,效果更佳且更持久,只使用tDCS也有较小的改善作用。有Meta分析显示^[63],AD患者在执行认知任务期间,“在线”施加刺激效果更显著。Cotelli等^[69]行左侧DLPFC阳极tDCS(2 mA, 25 min, 持续2周共10次)和个性化计算机记忆训练相结合,并未增强患者面孔-名字联想记忆训练的效果,即tDCS对记忆训练并无辅助作用。研究者认为原因主要是tDCS刺激参数不同。需要更多研究确定tDCS最优参数以及如何与认知训练相结合。

定量脑电图(quantitative electroencephalography, qEEG)显示,AD患者 θ 波增强, α 波和 β 波降低,且大脑后部 α 波和 β 波相干性降低。一项研究对7例可能AD患者行双侧额顶叶tDCS(1.5 mA, 15 min),同时患者执行词语再认任务,结果显示,基线期,AD患者 α 波和 β 波降低与较低的MMSE评分相关;阳极刺激后,TPC中 α 波和 β 波以及两者相干性升高,与工作记忆改善相关^[70]。

AD患者除记忆障碍外,还可表现为定向力、语言、注意力和执行功能等认知功能障碍。现有研究表明,tDCS可改善健康老年人的认知功能^[42-45]。是否可将tDCS应用于改善AD患者其他认知功能障碍,还需进一步研究。

3 安全性及不良反应

tDCS通常被认为安全、无明显副作用。大多数tDCS研究都基于安全操作规范指南选择合适刺激参数。tDCS的安全性主要取决于电流密度,即电流强度和电极片大小的比值;电流与皮肤接触可能出现皮肤刺激现象。受试者偶尔会报告副作用,如局部刺痛、瘙痒^[14,42,44-45]、灼痛、疼痛和头痛,其中瘙痒最常见,但通常副作用轻微,并在30~60 s内消失^[71],耐受性良好。研究中未发现不良反应^[43]或潜在不良反应,如心率、血压和情绪改变^[12]。研究未发现接受真假刺激的参与者在收缩压、舒张压、心率及情绪等生理指标上的差异,表明tDCS的舒适性和安全性^[72]。另外,tDCS设备相对便宜且便于携带,

可以在家等多种情况下使用。

4 展望

tDCS作为重要的神经调控手段,可改善老年人及AD患者的认知功能,安全、操作简单、低价和易携带,有广阔的应用前景。多种因素影响tDCS效果,包括年龄、性别、教育程度、健康状态、基因、大脑状态、基线任务表现^[73-74]、情绪和睡眠质量,且现有刺激方案不一。未来需要结合fMRI等影像学技术进一步明确tDCS的治疗机制,寻找精准的刺激靶点,选择个性化刺激模式。目前增强认知的方法还有高压氧、TMS、深部脑刺激等,如何结合这些疗法确定最佳干预方案,仍是未来的研究方向。结合TMS、脑电图、fMRI、单光子发射计算机断层成像和正电子发射断层成像术等,有助于进一步评估tDCS的效果和作用机制。

[参考文献]

- [1] Celsis P. Age-related cognitive decline, mild cognitive impairment or preclinical Alzheimer's disease? [J]. *Ann Med*, 2000, 32(1): 6-14.
- [2] Christensen P K, Doblhammer P G, Rau P R, et al. Ageing populations: the challenges ahead [J]. *Lancet*, 2009, 374(9696): 1196.
- [3] Mathers C D, Stevens G A, Boerma T, et al. Causes of international increases in older age life expectancy [J]. *Lancet*, 2015, 385(9967): 540-548.
- [4] Alzheimer's Association. 2018 Alzheimer's disease facts and figures [J]. *Alzheimers Dement*, 2018, 14(3): 367-429.
- [5] Shafqat S. Alzheimer disease therapeutics: perspectives from developing world [J]. *J Alzheimers Dis*, 2008, 15(2): 285-287.
- [6] 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 parameters [J]. *Brain Stimul*, 2016, 9(4): 501-517.
- [7] Giordano J, Bikson M, Kappenman E S, et al. Mechanisms and effects of transcranial direct current stimulation [J]. *Dose Response*, 2017, 15(1): 1559325816685467.
- [8] Hoffman R E, Cavus I. Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders [J]. *Am J Psychiatry*, 2002, 159(7): 1093.
- [9] Jamil A, Batsikadze G, Kuo H I, et al. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation [J]. *J Physiol*, 2017, 595(4): 1273-1288.
- [10] Hoy K E, Emonson M R, Arnold S L, et al. Testing the limits: investigating the effect of tDCS dose on working memory enhancement in healthy controls [J]. *Neuropsychologia*, 2013, 51(9): 1777-1784.
- [11] Martins A R, Fregni F, Simis M, et al. Neuromodulation as a cognitive enhancement strategy in healthy older adults: promises and pitfalls [J]. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, 2017, 24(2): 158-185.
- [12] Flöel A, Suttrop W, Kohl O, et al. Non-invasive brain stimulation improves object-location learning in the elderly [J]. *Neurobiol Aging*,

- 2012, 33(8): 1682.
- [13] Sandrini M, Manenti R, Brambilla M, et al. Older adults get episodic memory boosting from noninvasive stimulation of prefrontal cortex during learning [J]. *Neurobiol Aging*, 2016, 39: 210-216.
 - [14] Sandrini M, Brambilla M, Manenti R, et al. Noninvasive stimulation of prefrontal cortex strengthens existing episodic memories and reduces forgetting in the elderly [J]. *Front Aging Neurosci*, 2014, 6: 289.
 - [15] Manenti R, Brambilla M, Petesi M, et al. Enhancing verbal episodic memory in older and young subjects after non-invasive brain stimulation [J]. *Front Aging Neurosci*, 2013, 5: 49.
 - [16] Ross L A, McCoy D, Coslett H B, et al. Improved proper name recall in aging after electrical stimulation of the anterior temporal lobes [J]. *Front Aging Neurosci*, 2011, 3: 16.
 - [17] Kirova A M, Bays R B, Lagalwar S. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease [J]. *Biomed Res Int*, 2015, 2015(6): 1-9.
 - [18] Summers J J, Kang N, Cauraugh J H. Does transcranial direct current stimulation enhance cognitive and motor functions in the ageing brain? A systematic review and meta-analysis [J]. *Ageing Res Rev*, 2016, 25: 42-54.
 - [19] Pinal D, Zurrón M, Díaz F, et al. Stuck in default mode: inefficient cross-frequency synchronization may lead to age-related short-term memory decline [J]. *Neurobiol Aging*, 2015, 36(4): 1611-1618.
 - [20] Berryhill M E, Jones K T. tDCS selectively improves working memory in older adults with more education [J]. *Neurosci Lett*, 2012, 521(2): 148-151.
 - [21] Cabeza R, Anderson N D, Locantore J K, et al. Aging gracefully: compensatory brain activity in high-performing older adults [J]. *Neuroimage*, 2002, 17(3): 1394-1402.
 - [22] Davis S W, Dennis N A, Daselaar S M, et al. Que PASA? The posterior-anterior shift in aging [J]. *Cereb Cortex*, 2008, 18(5): 1201-1209.
 - [23] Buckner R L, Andrews-Hanna J R, Schacter D L. The brain's default network: anatomy, function, and relevance to disease [J]. *Ann N Y Acad Sci*, 2008, 1124(1): 1-38.
 - [24] Koch W, Teipel S, Mueller S, et al. Effects of aging on default mode network activity in resting state fMRI: does the method of analysis matter? [J]. *Neuroimage*, 2010, 51(1): 280-287.
 - [25] Grady C L, Protzner A B, Kovacevic N, et al. A multivariate analysis of age-related differences in default mode and task positive networks across multiple cognitive domains [J]. *Cereb Cortex*, 2010, 20(6): 1432.
 - [26] 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.
 - [27] Tusch E S, Alperin B R, Ryan E, et al. Changes in neural activity underlying working memory after computerized cognitive training in older adults [J]. *Front Aging Neurosci*, 2016, 8: e102710.
 - [28] van Dinteren R, Arns M, Jongsma M L, et al. Combined frontal and parietal P300 amplitudes indicate compensated cognitive processing across the lifespan [J]. *Front Aging Neurosci*, 2014, 6: 294.
 - [29] Cespon J, Rodella C, Rossini P M, et al. Anodal transcranial direct current stimulation promotes frontal compensatory mechanisms in healthy elderly subjects [J]. *Front Aging Neurosci*, 2017, 9: 420.
 - [30] Santarnecchi E, Brem A K, Levenbaum E, et al. Enhancing cognition using transcranial electrical stimulation [J]. *Curr Opin Behav Sci*, 2015, 4: 171-178.
 - [31] Passow S, Thurm F, Li S C. Activating developmental reserve capacity via cognitive training or non-invasive brain stimulation: potentials for promoting fronto-parietal and hippocampal-striatal network functions in old age [J]. *Front Aging Neurosci*, 2017, 9: 33.
 - [32] Elmasry J, Loo C, Martin D. A systematic review of transcranial electrical stimulation combined with cognitive training [J]. *Restor Neurol Neurosci*, 2015, 33(3): 263-278.
 - [33] Prehn K, Floel A. Potentials and limits to enhance cognitive functions in healthy and pathological aging by tDCS [J]. *Front Cell Neurosci*, 2015, 9: 355.
 - [34] Au J, Karsten C, Buschkuehl M, et al. Optimizing transcranial direct current stimulation protocols to promote long-term learning [J]. *J Cogn Enhanc*, 2017, 1(1): 65-72.
 - [35] Martin D M, Liu R, Alonzo A, et al. Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants [J]. *Int J Neuropsychopharmacol*, 2013, 16(9): 1927-1936.
 - [36] Park S H, Seo J H, Kim Y H, et al. Long-term effects of transcranial direct current stimulation combined with computer-assisted cognitive training in healthy older adults [J]. *Neuroreport*, 2014, 25(2): 122-126.
 - [37] Iachini I, Iavarone A, Senese VP, et al. Visuospatial memory in healthy elderly, AD and MCI: a review [J]. *Curr Aging Sci*, 2009, 2(1): 43-59.
 - [38] Antonenko D, Kulzow N, Sousa A, et al. Neuronal and behavioral effects of multi-day brain stimulation and memory training [J]. *Neurobiol Aging*, 2018, 61: 245-254.
 - [39] Kulzow N, Cavalcanti de Sousa A V, Cesarz M, et al. No effects of non-invasive brain stimulation on multiple sessions of object-location-memory training in healthy older adults [J]. *Front Neurosci*, 2017, 11: 746.
 - [40] Horvath J C, Forte J D, Carter O. Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS) [J]. *Brain Stimul*, 2015, 8(3): 535-550.
 - [41] Wang J X, Voss J L. Long-lasting enhancements of memory and hippocampal-cortical functional connectivity following multiple-day targeted noninvasive stimulation [J]. *Hippocampus*, 2015, 25(8): 877-883.
 - [42] Fertonani A, Brambilla M, Cotelli M, et al. The timing of cognitive plasticity in physiological aging: a tDCS study of naming [J]. *Front Aging Neurosci*, 2014, 6: 131.
 - [43] Meinzer M, Lindenberg R, Sieg M M, et al. Transcranial direct current stimulation of the primary motor cortex improves word-retrieval in older adults [J]. *Front Aging Neurosci*, 2014, 6: 253.
 - [44] Harty S, Robertson I H, Miniussi C, et al. Transcranial direct current stimulation over right dorsolateral prefrontal cortex enhances error awareness in older age [J]. *J Neurosci*, 2014, 34(10): 3646-3652.
 - [45] Learmonth G, Thut G, Benwell C S, et al. The implications of state-dependent tDCS effects in aging: Behavioural response is determined

- by baseline performance [J]. *Neuropsychologia*, 2015, 74: 108-119.
- [46] Kim Y J. Transcranial direct current stimulation as an alternative treatment in patients with Alzheimer's disease [J]. *Brain Neurorehabil*, 2017, 10(1): e4.
- [47] 梁宝今,梁涛,王晓文,等. 经颅直流电刺激对阿尔茨海默病认知功能的研究进展[J]. *中国康复医学杂志*, 2017, 32(8): 959-962.
- [48] 张凤霞,郑彩霞,黄晓琳. 经颅直流电刺激用于治疗阿尔茨海默病的研究进展[J]. *中国康复医学杂志*, 2017, 32(9): 1068-1073.
- [49] Jack C R Jr. Alliance for aging research AD biomarkers work group: structural MRI [J]. *Neurobiol Aging*, 2011, 32(Suppl 1): S48-S57.
- [50] Eichenbaum H. Prefrontal-hippocampal interactions in episodic memory [J]. *Nat Rev Neurosci*, 2017, 18(9): 547-558.
- [51] Polania R, Nitsche M A, Paulus W. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation [J]. *Hum Brain Mapp*, 2011, 32(8): 1236-1249.
- [52] Meinzer M, Lindenberger R, Phan M T, et al. Transcranial direct current stimulation in mild cognitive impairment: behavioral effects and neural mechanisms [J]. *Alzheimers Dement*, 2015, 11(9): 1032-1040.
- [53] Elder G J, Taylor J P. Transcranial magnetic stimulation and transcranial direct current stimulation: treatments for cognitive and neuropsychiatric symptoms in the neurodegenerative dementias? [J]. *Alzheimers Res Ther*, 2014, 6(9): 74.
- [54] Boggio P S, Khoury L P, Martins D C, et al. Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease [J]. *J Neurol Neurosurg Psychiatry*, 2009, 80(4): 444-447.
- [55] Boggio P S, Ferrucci R, Mameli F, et al. Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease [J]. *Brain Stimul*, 2012, 5(3): 223-230.
- [56] Ferrucci R, Mameli F, Guidi I, et al. Transcranial direct current stimulation improves recognition memory in Alzheimer disease [J]. *Neurology*, 2008, 71(7): 493-498.
- [57] Khedr E M, Gamal N F, El-Fetoh N A, et al. A double-blind randomized clinical trial on the efficacy of cortical direct current stimulation for the treatment of Alzheimer's disease [J]. *Front Aging Neurosci*, 2014, 6: 275.
- [58] Bystad M, Rasmussen I D, Gronli O, et al. Can 8 months of daily tDCS application slow the cognitive decline in Alzheimer's disease? A case study [J]. *Neurocase*, 2017, 23(2): 146-148.
- [59] Bystad M, Gronli O, Rasmussen I D, et al. Transcranial direct current stimulation as a memory enhancer in patients with Alzheimer's disease: a randomized, placebo-controlled trial [J]. *Alzheimers Res Ther*, 2016, 8(1): 13.
- [60] Liu C S, Rau A, Gallagher D, et al. Using transcranial direct current stimulation to treat symptoms in mild cognitive impairment and Alzheimer's disease [J]. *Neurodegener Dis Manag*, 2017, 7(5): 317-329.
- [61] Lee M S, Lee S H, Moon E O, et al. Neuropsychological correlates of the P300 in patients with Alzheimer's disease [J]. *Prog Neuropsychopharmacol Biol Psychiatry*, 2013, 40: 62-69.
- [62] Pedroso R V, Fraga F J, Corazza D I, et al. P300 latency and amplitude in Alzheimer's disease: a systematic review [J]. *Braz J Otorhinolaryngol*, 2012, 78(4): 126-132.
- [63] Hsu W Y, Ku Y, Zanto T P, et al. Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis [J]. *Neurobiol Aging*, 2015, 36(8): 2348-2359.
- [64] Vannini P, Hanseeuw B, Munro C E, et al. Hippocampal hypometabolism in older adults with memory complaints and increased amyloid burden [J]. *Neurology*, 2017, 88(18): 1759-1767.
- [65] Manenti R, Sandrini M, Gobbi E, et al. Strengthening of existing episodic memories through non-invasive stimulation of prefrontal cortex in older adults with subjective memory complaints [J]. *Front Aging Neurosci*, 2017, 9: 401.
- [66] Hampstead B, Gopinath K. Behavioral and fMRI changes associated with combined tDCS and cognitive rehabilitation in a case series of patients with mild cognitive impairment [J]. *Clin Neurophysiol*, 2013, 124(10): 123-124.
- [67] Penolazzi B, Bergamaschi S, Pastore M, et al. Transcranial direct current stimulation and cognitive training in the rehabilitation of Alzheimer disease: a case study [J]. *Neuropsychol Rehabil*, 2015, 25(6): 799-817.
- [68] Roncero C, Kniefel H, Service E, et al. Inferior parietal transcranial direct current stimulation with training improves cognition in amnestic Alzheimer's disease and frontotemporal dementia [J]. *Alzheimers Dement*, 2017, 3(2): 247-253.
- [69] Cotelli M, Manenti R, Brambilla M, et al. A nodal tDCS during face-name associations memory training in Alzheimer's patients [J]. *Front Aging Neurosci*, 2014, 6: 38.
- [70] Marceglia S, Mrakic-Sposta S, Rosa M, et al. Transcranial direct current stimulation modulates cortical neuronal activity in Alzheimer's disease [J]. *Front Neurosci*, 2016, 10: 134.
- [71] Kessler S K, Turkeltaub P E, Benson J G, et al. Differences in the experience of active and sham transcranial direct current stimulation [J]. *Brain Stimul*, 2012, 5(2): 155-162.
- [72] Floel A, Meinzer M, Kirstein R, et al. Short-term anomia training and electrical brain stimulation [J]. *Stroke*, 2011, 42(7): 2065-2067.
- [73] Benwell C S, Learmonth G, Miniussi C, et al. Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias [J]. *Cortex*, 2015, 69: 152-165.
- [74] Hsu T Y, Juan C H, Tseng P. Individual differences and state-dependent responses in transcranial direct current stimulation [J]. *Front Hum Neurosci*, 2016, 10: 643.

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