重复经颅磁刺激治疗阿尔茨海默病患者的疗效影响因素

王锦涛, 黄 蕾, 魏丽丽, 陈 炜

浙江大学医学院附属邵逸夫医院精神卫生科, 浙江 杭州 310016

[摘 要] 重复经颅磁刺激(rTMS)是一种安全的非侵入性干预技术,在改善阿尔茨海默病(AD)患者的认知功能上取得了一定的效果,不同rTMS治疗方案之间的疗效差异可能与其刺激频率、模式、部位、维持时间、强度、聚焦能力等因素有关。研究表明,高频rTMS的疗效优于低频;间接θ爆发刺激与常规rTMS疗效相当,但每次治疗时间短,患者依从性增加;刺激AD患者受损脑区或关联网络可增加疗效;短期强化治疗与长期维持治疗结合可维持疗效;结合认知损害程度动态调整刺激强度可增加疗效;利用磁共振功能连接方法等技术可解决rTMS的聚焦能力。本综述分析了上述影响因素,为今后rTMS治疗AD的临床方案设计提供思路。

[关键词] 阿尔茨海默病;重复经颅磁刺激;认知;治疗;影响因素;综述

[中图分类号] R749.1 [文献标志码] A

Factors affecting the efficacy of repetitive transcranial magnetic stimulation for patients with Alzheimer's disease

WANG Jintao, HUANG Lei, WEI Lili, CHEN Wei (Department of Psychiatry, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, China)
Corresponding author: CHEN Wei, E-mail: srrcw@zju.edu.cn, <https://orcid.org/0000-0003-0903-7945>

[Abstract] Repetitive transcranial magnetic stimulation (rTMS) is a safe and non-invasive technique. In recent years, many studies have demonstrated that rTMS can improve cognitive function in Alzheimer's disease (AD) patients and has potential as a therapeutic method for AD. However, the efficacy varies greatly with different rTMS treatment regimens, which is related to the frequency, type, location, duration, intensity and focusing power of stimulation. Recent studies have shown that high-frequency stimulation is superior to low-frequency stimulation; efficacy of intermittent theta burst

收稿日期:2021-02-25 接受日期:2021-05-20

基金项目:国家重点研发计划(2017YFC1310502);国家自然科学基金(2020C03021);浙江省重点研发计划(2020C03021)
第一作者:王锦涛,硕士研究生,主要从事阿尔茨海默病患者的脑功能研究;E-mail: wangjt@zju.edu.cn; <https://orcid.org/0000-0002-4649-7492>

通信作者:陈 炜,主任医师,硕士生导师,主要从事认知、情感、睡眠疾病诊治研究;E-mail: srrcw@zju.edu.cn; <https://orcid.org/0000-0003-0903-7945>

stimulation (iTBS) is similar to that of conventional rTMS, but iTBS treatment session is shorter and might be more acceptable for AD patients; rTMS stimulation sites targeting AD-damaged brain regions or associated networks would be more effective; short-term intensive treatment combined with long-term maintenance treatment can gain long-term efficacy; dynamic adjustment of stimulus intensity combined with the degree of cognitive impairment can enhance the efficacy; functional connection based on functional magnetic resonance imaging may improve the focusing power of rTMS. In this article, we review the factors related to the efficacy of rTMS, to provide reference for feasible rTMS therapeutic regimens of AD.

[**Key words**] Alzheimer's disease; Repetitive transcranial magnetic stimulation; Cognition; Therapy; Influence factor; Review

[J Zhejiang Univ (Med Sci), 2021, 50(3): 383-389.]

[**缩略语**] 阿尔茨海默病(Alzheimer disease, AD); 经颅磁刺激(transcranial magnetic stimulation, TMS); 重复经颅磁刺激(repetitive TMS, rTMS); 间接θ爆发刺激(intermittent theta burst stimulation, iTBS); 背外侧前额叶皮层(dorsolateral prefrontal cortex, DLPFC); 静息运动阈值(rest motor threshold, rMT); 静息态功能磁共振成像(resting-state functional magnetic resonance imaging, rs-fMRI)

AD是一种起病隐袭、进行性发展的神经退行性疾病,主要特征为早期出现记忆力下降,随着疾病的进展,逐渐出现两个及以上认知领域的其他损害,如执行功能、注意力、语言、社会认知和判断、心理运动速度、视觉操作或视觉空间能力,严重影响个体的日常生活独立性及生存质量,给社会、家庭带来沉重的经济和心理负担。据调查,我国AD患病率约为3.94%,患者人数已达到983万^[1]。2015年我国AD患者的年人均医疗费用约为13万元,预计2030年总医疗费用将达到约17万亿元^[2]。临床治疗AD的常用药物为乙酰胆碱酯酶抑制剂和N-甲基-D-门冬氨酸受体拮抗剂。这些药物虽然能在一定程度上改善AD患者的认知功能和延缓病程,但疗效有限,且部分患者无法耐受^[3]。针对β淀粉样蛋白的单克隆抗体虽能降低AD患者的β淀粉样蛋白沉积,但并不能改善患者的认知功能^[4-5]。我国最新上市的甘露特钠胶囊可能通过改变肠道菌群改善AD患者的认知功能,但还需要进行更多的相关研究以证实其疗效^[6]。截至目前,AD的新型药物开发几乎都以失败告终,而传统药物的使用存在诸多限制^[7]。因此,越来越多的研究者开始探索非药物治疗法。

TMS是一种安全、无创的非侵入性干预技术,其原理是根据电磁感应效应,通过在颅外施加由变化电场产生的变化磁场,穿过颅骨后在颅内产生感应电流,改变神经元膜电位,从而影响脑内物质代谢和神经元活动,引起脑功能变化^[8]。rTMS是在一段时间内,在大脑的特定区域以相同的强度传递一系列脉冲,从而对大脑产生一系列刺激,诱导持久作用,改变和调节皮层神经元的活动。因其具有安全、无创等优点,已广泛应用于抑郁症、强迫症、物质依赖、脑卒中等各种神经精神疾病的临床治疗。近年来,rTMS在AD治疗中已取得了一定疗效,可改善AD患者的认知功能和精神行为症状等^[9]。rTMS的安全性较好,常见不良反应为轻度头痛、耳鸣、短期听力下降、急性精神病症状等,癫痫的发生风险小于1/1000,且是在超出当前建议高频治疗参数的情况下发生^[10]。rTMS治疗AD未见癫痫等严重不良反应报道,少数受试者可能出现轻微头痛。但rTMS在AD治疗中的临床应用仍未成熟,各个研究的治疗方案及临床疗效差异较大,其治疗效果与刺激频率、模式、部位、强度、维持时间、聚焦能力等因素有关。本文就上述影响因素做一综述,为进一步促进rTMS未来的临床应用服务。

1 rTMS刺激频率和刺激模式与AD的疗效

rTMS刺激频率分为高频和低频。高频rTMS(刺激频率至少5 Hz)可使目标皮层的兴奋性提高,低频rTMS(刺激频率不超过1 Hz)则对目标皮层的兴奋性具有抑制作用^[11]。目前,rTMS在AD中的治疗大多选择高频。Ahmed等^[12]将45例AD患者随机分为3组,分别接受高频rTMS刺激(20 Hz)、低频rTMS刺激(1 Hz)或假刺激,结果显示高频组的工具性日常生活能力量表、简易精神状态检查和老年抑郁量表的改善程度明显优于低频组和假刺激组,且这种改善可维持3个月。荟萃分析结果也显示,高频rTMS治疗AD患者的有效性优于低频rTMS^[13-15]。目前高频rTMS多采用10 Hz或20 Hz,荟萃分析结果显示20 Hz的rTMS具有更好的改善认知功能效果^[15],但尚无对这两种刺激频率治疗AD患者疗效差异的研究,更高频率(如40 Hz)的rTMS是否能取得更好的疗效也需要临床研究来证实。高频rTMS可能可使AD患者的大脑皮层兴奋性提高,诱导突触的长时程增强,以达到认知功能的改善^[16]。AD患者的脑血流量和代谢偏低,而高频rTMS可提高脑代谢水平和脑血流,这可能也是高频刺激疗效较好的原因^[17-18]。

目前临床常用的rTMS刺激模式需要20~30 min^[19],这可能是影响AD患者疗效的一个因素。AD患者的配合程度比较差,很难做到长时间保持头部位置固定,而头部活动会导致rTMS刺激靶点的移动。iTBS是rTMS的一种特殊模式,其每次治疗只需几分钟,可减少靶点移动带来的误差^[20]。Wu等^[21]发现对左侧DLPFC作iTBS能显著改善AD患者的认知功能尤其是记忆功能。一项抑郁症的多中心研究发现iTBS与常规rTMS疗效相当^[22],但iTBS的费用约为常规rTMS的三分之二^[23],目前无AD患者的相关研究。iTBS具有治疗时间短、费用低的优势,今后应开展更多大样本、多中心iTBS治疗AD研究以明确其疗效。

2 rTMS刺激部位与AD的疗效

rTMS的作用方式有以下三种:直接靶向、距离效应和分布式调制。大多数rTMS研究都基于其直接靶向作用,即直接刺激某个功能障碍脑区,使该大脑区域受损的神经元活动得以调节,改善

其所支持的功能;距离效应是rTMS刺激与功能障碍脑区互相关联的神经区域,通过该区域与功能障碍脑区的相互作用来调节功能障碍脑区受损的神经元活动;分布式调制则是通过刺激诱导特定网络的神经递质释放来调节大脑活动,从而使异常活动的网络趋于正常^[24]。因此,刺激不同脑区可能带来不同的效果。早期的研究主要刺激DLPFC。Cotelli等^[25-26]在AD患者执行物体和动作图画命名任务过程中对其左侧或右侧DLPFC给予20 Hz的rTMS,发现rTMS能提高AD患者的命名准确性,改善认知功能。进一步研究发现,与假刺激相比,20 Hz的rTMS刺激左侧DLPFC两周可显著改善患者的听觉理解成绩,且这种效果可保持8周左右^[27]。Padala等^[28]发现10 Hz的rTMS刺激左侧DLPFC四周可改善AD患者的淡漠症状和认知功能,且对淡漠症状的改善持续至治疗结束后12周。一项纳入13个随机对照试验共293例AD患者的荟萃分析结果显示,左侧和右侧DLPFC的高频rTMS均可改善AD患者的认知功能^[29]。

除了DLPFC,研究者也探索了刺激其他脑区对AD患者的影响。用10 Hz的rTMS刺激右额下回和右额上回,发现刺激右额下回能改善AD患者的注意力、精神运动速度和执行功能^[30]。Koch等^[31]发现,rTMS刺激AD患者的楔前叶可以特异性地改善情景记忆功能;脑电图显示,rTMS治疗后患者楔前叶的神经活动增加, β 波段的脑部振荡增强,楔前叶与默认网络内侧额叶之间的功能连接增强。Alcala-Lozano等^[32]将刺激左侧DLPFC与刺激六个脑区(Broca区、Wernicke区、双侧DLPFC、双侧顶叶躯体感觉联合皮层)进行比较,发现疗效无差异。Cheng等^[14]的荟萃分析(8项研究,194例患者)结果也显示多靶点与单靶点的疗效无差异。但Lin等^[33]最近进行的一项荟萃分析(12项研究,231例患者)结果显示,多靶点刺激比单靶点治疗效果更好。今后需要开展大样本、多中心研究来验证。

综上,DLPFC是最先、也是在AD患者中实施rTMS刺激最多的脑区,rTMS不仅可改善DLPFC的局部脑活动,而且可改善其关联深部脑区或脑网络的神经活动,从而改善AD患者的认知功能^[34-35]。这一推测也在楔前叶中得到验证。Koch等^[31]发现楔前叶处rTMS可能通过改善其局部和所在默认网络的神经活动,从而改善AD患者

的记忆功能。AD是一种多脑区、多脑网络、多种认知领域受损的神经退行性疾病^[36],rTMS刺激多个脑区可能具有较好的疗效,但由于rTMS的距离效应和网络效应,必须考虑多个脑区之间的相互作用,以免产生拮抗作用。盲目刺激多个脑区,一方面可能会导致不同脑区之间的刺激作用互相拮抗,另一方面也可能会刺激无效脑区。因此针对AD受损脑区或关联网络,寻找最有效刺激点进行rTMS刺激的方案可能更合适。

3 rTMS刺激维持时间、刺激强度与AD的疗效

rTMS刺激效应的维持时间与刺激时长成正比,即刺激时间越长,刺激效应的维持时间越长^[11]。荟萃分析结果显示,长期rTMS(超过5次)比短期rTMS(少于3次)对AD患者认知功能的改善有更好的作用^[33]。Cotelli等^[27]发现10次和20次左侧DLPFC的rTMS均可改善AD患者的听觉理解成绩,且均可保持8周左右。最近一项纳入75例患者的研究显示,20 Hz左侧DLPFC的rTMS治疗6周(5次/周)后,AD患者的认知功能改善,其中简易精神状态检查评分的改善可维持12周左右,皮质可塑性的提高与rTMS治疗AD患者的认知改善相关^[37]。研究者对AD患者先进行6周rTMS结合认知训练的强化治疗(5次/周),再进行3个月的维持治疗(2次/周),发现患者认知功能均有显著改善^[38-39]。rTMS刺激效应的维持时间与刺激时长成正比的原因可能与长时程增强有关,刺激时长越久,长时程增强效应更强更持久^[40]。虽然有研究显示10次和20次rTMS的疗效维持时间相当,但较长的刺激时间一般会使疗效维持时间更久。因此,先进行短时间的rTMS强化治疗以快速取得治疗效果,后进行长期rTMS维持治疗以维持疗效可能成为未来的趋势。

在刺激强度方面,临床采用静息状态时TMS作用于运动皮层引起所支配肌肉收缩的最小强度,即rMT,通常以80%~120% rMT的某一个强度给患者治疗。健康受试者给予50%、75%、100%的rMT刺激,其N-back任务的认知成绩提高,反应时间缩短,其中以75%的rMT最显著^[41]。另一项研究采用60%、80%、100%、120%的rMT刺激,发现脑皮层的兴奋性与刺激强度呈依赖效应^[42]。在AD患者中,不同皮质之间的功能连接通常遭到破坏。有研究显示,90% rMT的TMS刺激健康受试

者的顶叶能提高其运动皮层的兴奋性,但在AD患者中需要110%的rMT强度,而且运动皮层兴奋性与认知功能表现成正比,提示认知性能较好患者的功能连接受损较小,所需的rMT强度较小^[43]。因此,最佳rTMS刺激强度可能与患者的认知功能有关,今后应进一步明确不同刺激强度与rTMS治疗AD疗效的关系,开发动态调整刺激强度治疗不同认知功能损害AD的方法。

4 rTMS聚焦能力与AD的疗效

海马是参与情景记忆形成的重要脑部结构,同时也参与其他认知功能的产生,是AD患者最先产生病变的脑区^[44-46]。要提高AD的治疗效果,直接或间接刺激海马非常关键。研究发现,通过植入的深部脑电极直接刺激海马体可显著改善记忆功能^[47-48],但此方法费用高、有创,并不适合AD患者。由于海马位于大脑深处,而常用的rTMS治疗仪是“8”字线圈,其聚焦点在3 cm或更浅,只能聚焦于大脑皮层(2 cm),无法刺激深部脑组织;深部TMS刺激可达6 cm,可解决聚焦深度的问题,且不损伤浅层皮质,高效刺激大脑深部核团,但目前深部TMS的刺激线圈为H型,只能刺激脑岛等深部脑区,仍无法刺激海马^[49-51]。

为了克服这一困难,Wang等^[52]发明了一种间接的刺激方法,即通过刺激网络中的节点,将该节点的刺激效应传输到网络内的其他节点。基于皮质-海马网络,研究者在rs-fMRI引导下,使用高频rTMS个体化刺激顶叶皮层来干预海马的神经活动,发现健康受试者经rTMS刺激后不但记忆功能显著提高,而且海马及其网络的神经活动也得到了显著增强。这一研究方法和结论已经在健康受试者或认知损伤患者中得到了验证^[53-58]。Velioglu等^[59]发现,个体化刺激顶叶的海马靶向rTMS可以提高AD患者的视觉识别记忆功能和时钟绘制测试分数。本研究团队初步研究发现,在rs-fMRI引导下个体化刺激顶叶的海马靶向rTMS可以改善AD患者的记忆和整体认知功能^[60],并且这种改善与海马脑血流量、默认网络内功能连接强度增加相关,提示rTMS可调节海马神经活动和默认网络内功能连接,从而改善AD患者记忆功能和整体认知功能(待发表)。针对AD受损脑区或关联网络进行功能连接定位的rTMS刺激可能成为未来的趋势。

5 结 语

rTMS作为AD的非药物治疗方法,在改善AD患者认知功能、记忆等方面已取得较好的效果。已有研究表明,频率为10~20 Hz、强度为90%~120% rMT的rTMS刺激AD患者DLPFC、楔前叶、左顶叶等脑区1~6周,能改善患者的认知功能,且疗效能维持一段时间;高频疗效优于低频,可进一步探索更高频率(如40 Hz)的rTMS疗效;iTBS具有治疗时间短、费用低等优势,可以进一步研究其与rTMS的疗效差异;持续较长的刺激时间会使疗效维持时间更久,随着rTMS治疗仪器逐步家庭化,短期强化治疗结合长期维持治疗的方案具有广阔的前景;最佳刺激强度与患者的认知功能有关,今后可根据患者认知损害程度的变化动态调整刺激强度,并且可基于磁共振功能连接方法等技术解决rTMS的聚焦能力,针对AD受损脑区或关联网络进行个体化的有效刺激。

建议今后聚焦下列问题:①rTMS治疗AD的效果主要取决于刺激靶点、频率、模式、强度、治疗时间等因素,如何理清这些因素与疗效的关系,解决靶点定位技术手段模糊、定位准确性差等关键问题,利用磁共振导航等技术精确定位,提高rTMS临床疗效。②目前临床研究样本量小,随机双盲试验少,普遍缺乏多中心、长期跟踪研究,今后应开展多中心、大样本、前瞻性研究,提高rTMS治疗AD疗效的证据等级。③rTMS存在聚焦能力不足,常用的“8”字线圈及H型线圈无法满足AD治疗的需要,须进一步研发与深部TMS配套的线圈、基于磁共振功能连接方法等技术。④从动物模型、尸体解剖及临床各方面采用分子生物学、细胞生物学、影像学、电生理等相关技术,阐明rTMS治疗AD的相关机制。⑤建立实时、动态的个体化治疗技术和方案。由于不同AD患者脑皮层活动各不相同,疾病的严重程度、临床表现、共病躯体疾病、遗传等因素各不相同,临床疗效差异显著,应对相关因素进行综合分析,通过人工智能等信息技术建立模型,实施个体化治疗方案。相信随着基础研究和临床应用的不断深入,rTMS将为AD患者带来福音。

利益冲突 所有作者均声明不存在利益冲突

参考文献

- [1] JIA L, DU Y, CHU L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study[J/OL]. **Lancet Public Health**, 2020, 5(12): e661-e671.
- [2] JIA J, WEI C, CHEN S, et al. The cost of Alzheimer's disease in China and re-estimation of costs worldwide[J]. **Alzheimers Dement**, 2018, 14(4): 483-491.
- [3] KRANTIC S. Editorial: from current diagnostic tools and therapeutics for Alzheimer's disease towards earlier diagnostic markers and treatment targets[J]. **Curr Alzheimer Res**, 2017, 14(1): 2-5.
- [4] VANDENBERGHE R, RINNE J O, BOADA M, et al. Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials[J]. **Alzheimers Res Ther**, 2016, 8(1): 18.
- [5] KITAMURA S, NAKAMURA Y, HOMMA A, et al. Tolerability and efficacy of the long-term administration of memantine hydrochloride (Memary®) in patients with moderate to severe Alzheimer's disease[J]. **Nippon Ronen Igakkai Zasshi**, 2014, 51(1): 74-84.
- [6] XIAO S, CHAN P, WANG T, et al. A 36-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial of sodium oligomannate for mild-to-moderate Alzheimer's dementia[J]. **Alzheimers Res Ther**, 2021, 13(1): 62.
- [7] CUMMINGS J, LEE G, RITTER A, et al. Alzheimer's disease drug development pipeline: 2019[J]. **Alzheimers Dement**, 2019, 5(1): 272-293.
- [8] WASSERMANN E M, LISANBY S H. Therapeutic application of repetitive transcranial magnetic stimulation: a review[J]. **Clin NeuroPhysiol**, 2001, 112(8): 1367-1377.
- [9] LEFAUCHEUR J P, ALEMAN A, BAEKEN C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018)[J]. **Clin NeuroPhysiol**, 2020, 131(2): 474-528.
- [10] GONSALVEZ I, BAROR R, FRIED P, et al. Therapeutic noninvasive brain stimulation in Alzheimer's disease[J]. **Curr Alzheimer Res**, 2017, 14(4): 362-376.
- [11] KLOMJA W, KATZ R, LACKMY-VALLÉE A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS)[J]. **Ann Phys Rehabil Med**, 2015, 58(4): 208-213.
- [12] AHMED M A, DARWISH E S, KHEDR E M, et al. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia[J]. **J Neurol**, 2012, 259(1): 83-92.
- [13] LIAO X, LI G, WANG A, et al. Repetitive transcranial magnetic stimulation as an alternative therapy for cognitive impairment in Alzheimer's disease: a meta-analysis[J]. **J Alzheimer Dis**, 2015, 48(2): 463-472.
- [14] 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/OL]. *Int J Geriatr Psychiatry*, 2018, 33(1): e1-e13.
- [15] WANG X, MAO Z, LING Z, et al. Repetitive transcranial magnetic stimulation for cognitive impairment in Alzheimer's disease: a meta-analysis of randomized controlled trials[J]. *J Neurol*, 2020, 267(3): 791-801.
 - [16] ESSER S K, HUBER R, MASSIMINI M, et al. A direct demonstration of cortical LTP in humans: a combined TMS/EEG study[J]. *Brain Res Bull*, 2006, 69(1): 86-94.
 - [17] AUSTIN B P, NAIR V A, MEIER T B, et al. Effects of hypoperfusion in Alzheimer's disease[J]. *J Alzheimer Dis*, 2011, 26 Suppl 3: 123-133.
 - [18] GUSE B, FALKAI P, WOBROCK T. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review[J]. *J Neural Transm*, 2010, 117(1): 105-122.
 - [19] LEFAUCHEUR J P, ANDRÉ-OBADIA N, ANTAL A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)[J]. *Clin NeuroPhysiol*, 2014, 125(11): 2150-2206.
 - [20] HUANG Y Z, EDWARDS M J, ROUNIS E, et al. Theta burst stimulation of the human motor cortex[J]. *Neuron*, 2005, 45(2): 201-206.
 - [21] WU X, JI G J, GENG Z, et al. Strengthened theta-burst transcranial magnetic stimulation as an adjunctive treatment for Alzheimer's disease: an open-label pilot study[J]. *Brain Stimulation*, 2020, 13(2): 484-486.
 - [22] BLUMBERGER D M, VILA-RODRIGUEZ F, THORPE K E, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial[J]. *Lancet*, 2018, 391(10131): 1683-1692.
 - [23] MENDLOWITZ A B, SHANBOUR A, DOWNAR J, et al. Implementation of intermittent theta burst stimulation compared to conventional repetitive transcranial magnetic stimulation in patients with treatment resistant depression: a cost analysis[J/OL]. *PLoS One*, 2019, 14(9): e0222546.
 - [24] ROTENBERG A, HORVATH J C, PASCUAL-LEONE A. *Transcranial magnetic stimulation*[M]. New York: Springer, 2014: 235-257.
 - [25] COTELLI M, MANENTI R, CAPPAS F, et al. Effect of transcranial magnetic stimulation on action naming in patients with Alzheimer disease[J]. *Arch Neurol*, 2006, 63(11): 1602-1604.
 - [26] COTELLI M, MANENTI R, CAPPAS F, et al. Transcranial magnetic stimulation improves naming in Alzheimer disease patients at different stages of cognitive decline[J]. *Eur J Neurol*, 2008, 15(12): 1286-1292.
 - [27] COTELLI M, CALABRIA M, MANENTI R, et al. Improved language performance in Alzheimer disease following brain stimulation[J]. *J Neurol Neurosurg Psychiatry*, 2011, 82(7): 794-797.
 - [28] PADALA P R, BOOZER E M, LENSING S Y, et al. Neuromodulation for apathy in Alzheimer's disease: a double-blind, randomized, sham-controlled pilot study[J]. *J Alzheimer Dis*, 2020, 77(4): 1483-1493.
 - [29] CHOU Y H, TON THAT V, SUNDMAN M. A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease[J]. *NeuroBiol Aging*, 2020, 86: 1-10.
 - [30] ELIASOVA I, ANDERKOVA L, MARECEK R, et al. Non-invasive brain stimulation of the right inferior frontal gyrus may improve attention in early Alzheimer's disease: a pilot study[J]. *J Neurological Sci*, 2014, 346(1-2): 318-322.
 - [31] KOCH G, BONNÌ S, PELLICCIARI M C, et al. Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease[J]. *NeuroImage*, 2018, 169: 302-311.
 - [32] ALCALÁ-LOZANO R, MORELOS-SANTANA E, CORTÉS-SOTRES J F, et al. Similar clinical improvement and maintenance after rTMS at 5 Hz using a simple vs. complex protocol in Alzheimer's disease[J]. *Brain Stimul*, 2018, 11(3): 625-627.
 - [33] LIN Y, JIANG W J, SHAN P Y, et al. The role of repetitive transcranial magnetic stimulation (rTMS) in the treatment of cognitive impairment in patients with Alzheimer's disease: a systematic review and meta-analysis[J]. *J Neurol Sci*, 2019, 398: 184-191.
 - [34] NARDONE R, SEBASTIANELLI L, VERSACE V, et al. TMS-EEG co-registration in patients with mild cognitive impairment, Alzheimer's disease and other dementias: a systematic review[J]. *Brain Sci*, 2021, 11(3): 303.
 - [35] HIMORI T, NAKAJIMA S, MIYAZAKI T, et al. Effectiveness of the prefrontal repetitive transcranial magnetic stimulation on cognitive profiles in depression, schizophrenia, and Alzheimer's disease: a systematic review[J]. *Prog Neuro-PsychoPharmacol Biol Psychiatry*, 2019, 88: 31-40.
 - [36] ZHOU J, SEELEY W W. Network dysfunction in Alzheimer's disease and frontotemporal dementia: implications for psychiatry[J]. *Biol Psychiatry*, 2014, 75(7): 565-573.
 - [37] LI X, QI G, YU C, et al. Cortical plasticity is correlated with cognitive improvement in Alzheimer's disease patients after rTMS treatment[J]. *Brain Stimul*, 2021, 14(3): 503-510.
 - [38] BENTWICH J, DOBRONEVSKY E, AICHENBAUM S, et al. Beneficial effect of repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease: a proof of

- concept study[J]. **J Neural Transm**, 2011, 118(3): 463-471.
- [39] RABEY J M, DOBRONEVSKY E, AICHENBAUM S, et al. Repetitive transcranial magnetic stimulation combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: a randomized, double-blind study[J]. **J Neural Transm**, 2013, 120(5): 813-819.
- [40] LUBER B, LISANBY S H. Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS)[J]. **NeuroImage**, 2014, 85: 961-970.
- [41] CHUNG S W, ROGASCH N C, HOY K E, et al. Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance[J]. **Hum Brain Mapp**, 2018, 39(2): 783-802.
- [42] KÄHKÖNEN S, KOMSSI S, WILENIUS J, et al. Prefrontal transcranial magnetic stimulation produces intensity-dependent EEG responses in humans[J]. **NeuroImage**, 2005, 24(4): 955-960.
- [43] BONNÌ S, LUPO F, LO GERFO E, et al. Altered parietal-motor connections in Alzheimer's disease patients[J]. **J Alzheimer Dis**, 2012, 33(2): 525-533.
- [44] PRESTON A R, EICHENBAUM H. Interplay of hippocampus and prefrontal cortex in memory[J]. **Curr Biol**, 2013, 23(17): R764-R773.
- [45] OLSEN R K, MOSES S N, RIGGS L, et al. The hippocampus supports multiple cognitive processes through relational binding and comparison[J]. **Front Hum Neurosci**, 2012, 6: 146.
- [46] BALLARD C, GAUTHIER S, CORBETT A et al. Alzheimer's disease[J]. **Lancet**, 2011, 377: 1019-1031.
- [47] SUTHANA N, HANEED Z, STERN J, et al. Memory enhancement and deep-brain stimulation of the entorhinal area[J]. **N Engl J Med**, 2012, 366(6): 502-510.
- [48] JUN S, KIM J S, CHUNG C K. Direct stimulation of human hippocampus during verbal associative encoding enhances subsequent memory recollection[J]. **Front Hum Neurosci**, 2019, 13: 23.
- [49] ROTH Y, AMIR A, LEVKOVITZ Y, et al. Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils[J]. **J Clin NeuroPhysiol**, 2007, 24(1): 31-38.
- [50] ROTH Y, PELL G S, CHISTYAKOV A V, et al. Motor cortex activation by H-coil and figure-8 coil at different depths. Combined motor threshold and electric field distribution study[J]. **Clin NeuroPhysiol**, 2014, 125(2): 336-343.
- [51] LU M, UENO S. Comparison of the induced fields using different coil configurations during deep transcranial magnetic stimulation[J/OL]. **PLoS One**, 2017, 12(6): e0178422.
- [52] WANG J X, ROGERS L M, GROSS E Z, et al. Targeted enhancement of cortical-hippocampal brain networks and associative memory[J]. **Science**, 2014, 345(6200): 1054-1057.
- [53] WANG H, JIN J, CUI D, et al. Cortico-hippocampal brain connectivity-guided repetitive transcranial magnetic stimulation enhances face-cued word-based associative memory in the short term[J]. **Front Hum Neurosci**, 2020, 14: 541791.
- [54] CUI X, REN W, ZHENG Z, et al. Repetitive transcranial magnetic stimulation improved source memory and modulated recollection-based retrieval in healthy older adults[J]. **Front Psychol**, 2020, 11: 1137.
- [55] FREEDBERG M, REEVES J A, TOADER A C, et al. Optimizing hippocampal-cortical network modulation via repetitive transcranial magnetic stimulation: a dose-finding study using the continual reassessment method[J]. **Neuromodulation**, 2020, 23(3): 366-372.
- [56] FREEDBERG M, REEVES J A, TOADER A C, et al. Persistent enhancement of hippocampal network connectivity by parietal rtms is reproducible[J]. **eNeuro**, 2019, 6(5): ENEURO.0129-19.2019
- [57] HERMILLER M S, KARP E, NILAKANTAN A S, et al. Episodic memory improvements due to noninvasive stimulation targeting the cortical-hippocampal network: a replication and extension experiment[J/OL]. **Brain Behav**, 2019, 9(12): e01393.
- [58] TAYLOR J L, HAMBRO B C, STROSSMAN N D, et al. The effects of repetitive transcranial magnetic stimulation in older adults with mild cognitive impairment: a protocol for a randomized, controlled three-arm trial[J]. **BMC Neurol**, 2019, 19(1): 326.
- [59] VELIOGLU H A, HANOGLU L, BAYRAKTAROGU Z, et al. Left lateral parietal rTMS improves cognition and modulates resting brain connectivity in patients with Alzheimer's disease: possible role of BDNF and oxidative stress[J]. **NeuroBiol Learn Mem**, 2021, 180: 107410.
- [60] JIA Y, XU L, YANG K, et al. Precision repetitive transcranial magnetic stimulation over the left parietal cortex improves memory in Alzheimer's disease: a randomized, double-blind, sham-controlled study[J]. **Front Aging Neurosci**, 2021, 13: 693611.

[本文编辑 李璐余方]