

重复经颅磁刺激治疗阿尔茨海默病认知障碍作用机制研究进展

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摘要

阿尔兹海默病(Alzheimer's disease, AD)是一种神经退行性疾病, 患者会出现认知功能下降、记忆丧失和行为改变等各种症状。由于AD的病因以及发病机制未明, 因此没有有效的治疗药物。最近几年, 重复经颅磁刺激(repeated transcranial magnetic stimulation, rTMS)作为一种新型的治疗手段受到许多学者的关注。rTMS可以通过多种途径来改善AD患者的认知障碍。本文对近年来rTMS治疗AD机制的相关研究进行了系统综述, 旨在为治疗AD提供新的思路。

关键词

重复经颅磁刺激, 阿尔茨海默病, 机制

Research Advances in the Mechanism of Action of Repetitive Transcranial Magnetic Stimulation in Treating Cognitive Impairment in Patients with Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease in which patients suffer from various symptoms such as cognitive decline, memory loss and behavioral changes. Since the etiology as well as the pathogenesis of AD is unknown, there are no effective therapeutic drugs. In recent years, repeated transcranial magnetic stimulation (rTMS) has attracted much attention as a novel therapeutic tool. rTMS can improve the cognitive deficits of AD patients through various ways. This paper provides a systematic review of the relevant studies on the mechanism of rTMS in the treatment of AD in recent years, aiming to provide new ideas for the treatment of AD.

Keywords

Repetitive Transcranial Magnetic Stimulation, Alzheimer Disease, Mechanism

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1. 引言

阿尔兹海默病(Alzheimer's disease, AD)是一种与年龄相关的慢性神经系统退行性疾病,以认知功能障碍和记忆力减退为主要症状,俗称老年痴呆。目前老龄化现象逐渐加重,AD发病率也逐年呈上升的趋势,2018年全球痴呆症人口总数已达5000万,2015年我国痴呆人数已多达950万,是世界上痴呆症患者人数最多的国家[1],这将给整个社会带来巨大的负担,因此寻找有效的治疗方法迫在眉睫。由于目前AD的临床治疗单一且有限,因此探索和研究积极的、能够有效控制和延缓痴呆发生的非药物干预措施,成为近年来国内外学者的主要研究方向[2]。

经颅磁刺激(transcranial magnetic stimulation, TMS)是一种通过电磁感应对大脑进行电刺激的安全无创手段[3]。重复经颅磁刺激(repeated transcranial magnetic stimulation, rTMS)为TMS的治疗模式之一,它使用快速变化的磁场来调节大脑的电活动[4]。rTMS正在成为对抗阿尔兹海默病的一种非侵入性治疗策略[5]。大量临床研究表明rTMS是一种有前途的轻中度AD治疗方法[6]-[8]。近年研究表明,rTMS可通过多靶点机制改善AD病理,包括抑制A β 沉积、调节突触功能及抗炎作用等。本文系统综述rTMS干预AD的分子与网络机制研究进展,以期临床转化提供理论依据。

2. rTMS对AD的作用机制

2.1. rTMS可减少A β 沉积

AD主要的临床病理特征是在大脑中出现由A β 的肽组成的神经炎性斑块和由称为tau的蛋白组成的神经原纤维缠结(neurofibrillary tangles, NFT)[9][10],因此,降低A β 、磷酸化tau蛋白水平可改善AD的症状。要想减少A β ,则需对A β 从“来”和“去”入手[11]。A β 是 β 位淀粉样前体蛋白裂解酶1和 γ 分泌酶切割淀粉样前体蛋白(amyloid precursor pro-teins, APP)的产物[12]。Huang等[13]研究报道了低频rTMS可以通过减少APP23/PS45双转基因AD小鼠的 β -位点APP裂解酶1(BACE1)和APP来降低A β 水平。Choung等[14]研究报道了在将HT-22细胞(小鼠海马细胞系)与A β 42一起孵育的模拟体外AD模型中,重复磁刺激(rMS)可下调淀粉样蛋白 β 的表达水平。Tao亦等[15]研究发现在被诊断为AD的患者

随机接受 20 Hz rTMS 治疗左侧背外侧前额叶皮质(DLPFC)或假刺激后, 在第 3、4 和 6 周, rTMS 组的血清 A β 40、A β 42 以及总 A β 水平显著低于假刺激组。以上的研究均是从“来源”入手进行的研究。从“去路”入手进行研究, 我们发现 rTMS 促进了伽马波段(40 Hz)的神经元振荡, 阿尔茨海默病 γ 活性的增加已被证明可加速淀粉样斑块的清除, 并增加小胶质细胞的活化[16]。Lin 亦从“去路”着手进行报道了在 4 至 5 个月大的 5xFAD 小鼠模型中, 高频 rTMS 治疗显著提高了脑清除途径的引流效率, 包括脑实质中的淋巴系统和脑膜淋巴管, 在 rTMS 治疗的 5xFAD 小鼠的前额叶皮层和海马中观察到 A β 沉积的显著减少[17]。

2.2. rTMS 可减少 Tau 蛋白高磷酸化

Tau 蛋白与微管相关并稳定轴突和树突中的微管。Tau 经历翻译后修饰的过程, 特别是过度磷酸化[18]。高度磷酸化的 tau 蛋白(P-tau)积聚并形成细胞内神经原纤维缠结(NFT)。NFTs 诱导炎症反应并引起神经毒性。因此, 降低 P-tau 可作为预防 AD 的潜在靶点之一。影响 tau 蛋白磷酸化的因素最重要的就是蛋白激酶活性的增强。其中 Wnt/ β -catenin 信号通路的重要组分是糖原合成酶激酶 3 β (glycogen synthase kinase-3 β , GSK-3 β), 可以磷酸化 AD 患者脑中几乎所有的 tau 蛋白[19]。因此, 基于 GSK-3 β 对 tau 蛋白磷酸化的重要作用, Liu 等[20]研究通过 AD 小鼠模型证明, 10Hz 高频 rTMS 可抑制 GSK-3 β 活性, 减少 tau 蛋白 Ser396 位点的磷酸化, 改善神经元微管稳定性, 机制涉及 PI3K/Akt 通路介导的 GSK-3 β 磷酸化失活, 来达到改善 AD 的目的。亦有[21]研究显示, 在 3xTg-AD 小鼠中, 10 Hz rTMS 干预显著下调皮质 GSK-3 β 活性, 恢复突触可塑性和微管相关蛋白(如 MAP2)的表达, 修复微管结构完整性, 改善空间记忆缺陷。此外, Zhang 等[22]研究发现使用 10 Hz rTMS 刺激 AD 患者左侧 DLPFC 和左侧颞叶区后, AD 患者血浆中微小核糖核酸-125b (miR-125b)浓度上调, 血浆磷酸化 Tau-181 蛋白(P-tau181)浓度下调, 从而改善 AD 患者的认知功能。

2.3. rTMS 抑制细胞凋亡并发挥神经保护作用

在神经退行性疾病中, 尤其是 AD, 过度的神经元损失被认为是常见的, 并归因于凋亡, 凋亡是神经元的主要细胞死亡途径[23] [24]。在 AD 中, 凋亡相关的 Bcl-2 水平下调, 而 Bax 和裂解的 caspase-3 水平上调[25]。TMS 非侵入性地调节和平衡凋亡途径, 对 AD 患者的大脑产生有益影响。Chen 等[26]研究表明在 AD 症状的诱导 β 1-42 增加了脑组织中凋亡细胞的数量。随着凋亡细胞数量的增加, 裂解的 caspase-3 和 Bax 的水平增加, 而 Bcl-2 的水平被抑制。用 rTMS 处理后, 凋亡细胞的数量被显著抑制和凋亡相关成员的表达模式被逆转。亦有研究表明, rTMS 抑制细胞凋亡和细胞凋亡途径, 因此, rTMS 可以改善认知障碍, 并对受影响大脑中的神经元发挥神经保护作用, 特别是在 AD [27]。rTMS 可调节 Bcl-2 和 Bax 的表达, 从而促进认知障碍的功能恢复, 并通过提高突触可塑性来增强学习和记忆的保护机制; 这一机制可能由 BDNF 信号通路介导。未来尚需要更多的研究来研究 TMS 对 AD 病理学中细胞凋亡的影响。

2.4. rTMS 促进突触可触性和海马神经发生

突触可塑性(synaptic plasticity)是指突触的形态和功能在外界环境的影响下发生持久变化的现象。其主要有两种体现形式: 长时程增强(longterm potentiation, LTP)和长时程抑制(long-term de-pression, LTD), 二者的动态调节可以作为学习记忆得以正常运转的基础[28]。海马神经元突触可塑性的调节是 rTMS 最广泛接受的机制。rTMS 刺激的调节作用取决于刺激的频率, 即低频刺激导致兴奋性突触后电位振幅降低并产生 LTD 效应, 反之, 高频刺激可导致兴奋性突触后电位振幅增加并产生 LTP 效应。大量的体外和体内实验模型证明 rTMS 可以增加 LTP [29]。特别相关的是, 这已经在各种痴呆鼠模型中得到证明, 其中 rTMS 挽救 LTP 缺陷[30]-[33], 并且这些神经可塑性的改善与海马依赖的空间认知测量的性能改善有关[13]

[34]。此外, 在 AD 的鼠模型中观察到 rTMS 治疗后 LTP 的增加和空间认知的改善伴随着 β 淀粉样蛋白负荷的减少, 并且已报道的通过 rTMS 解释这种病理学减少的机制包括淀粉样前体蛋白(APP)的减少[13]和通过增加 Homer1a 支架蛋白的表达来促进大电导钙激活钾通道[31]。在更细的水平上, 有许多 rTMS 诱导的效应可能介导突触功能的增强来实现。例如, 许多研究报道, 在 rTMS 治疗后海马源性神经营养因子(BDNF)和血管内皮生长因子(VEGF)的表达增加[35]-[37]。据报道, 除了这些神经营养因子, rTMS 还增加了 n-甲基-D-天冬氨酸(NMDA)受体和其他促进突触可塑性的蛋白质的表达, 如突触素、突触后密度蛋白-95、细胞周期蛋白依赖性激酶 5、生长相关蛋白 43 (GAP43)的表达[38]-[42]。并且有研究报道称 rTMS 增加了齿状回的海马神经发生[43], 它在模式分离中起着关键作用[44]。除了上面列出的神经营养介质, rTMS 还可能通过增加胆囊收缩素(CCK)的表达促进神经发生[36]。这些实验结果均证实 rTMS 调节 AD 患者的突触可塑性及神经发生来改善 AD 患者的行为障碍。

2.5. rTMS 调节神经递质及促进 N-甲基-D-天冬氨酸受体表达

神经递质, 如多巴胺、谷氨酸、天冬氨酸及 γ -氨基丁酸(GABA), 是调控认知功能、学习记忆等高级神经活动的重要信号分子[45]。当其代谢过程或表达水平发生异常时, 可能引发突触传递效率下降、认知调控能力受损以及学习记忆功能缺陷等病理表现。AD 的特征是海马和新皮层中神经递质如乙酰胆碱和谷氨酸盐的浓度显著降低[46]。许多研究强调, 神经递质和受体的表达在 AD 患者中明显减少[47] [48]。因此, 以神经递质及其受体为干预靶点或是治疗 AD 的潜在策略。多巴胺作为一种由多巴胺能神经元分泌的单胺类递质, 不仅参与突触可塑性调控, 还对情绪稳定、认知及运动功能具有调节作用[49]。其受体家族(D1-D5 亚型)在边缘系统与皮质区域呈现显著富集分布特征[50]。多巴胺能系统在 AD 的病理生理学中起着关键作用[51]。在 AD 患者中经常报告多巴胺含量及其受体的损失和减少, 导致运动障碍和认知下降[52] [53]。TMS 增加了 AD 患者多巴胺和多巴胺受体的水平。在 Choung 等人的一项研究结果表明, 高频 rTMS 和低频 rTMS 增加了海马体中的多巴胺水平。相较于低频刺激及假刺激组, 高频 rTMS 干预可显著提升阿尔茨海默病模型脑区海马及皮层中多巴胺 D4 受体的表达水平。N-甲基-D-天冬氨酸受体(NMDAR)作为突触功能调控的核心分子, 直接参与突触信号传递、可塑性维持以及海马 LTP 等过程, 是学习记忆等高级认知功能的分子基础[54]。在 AD 中, $A\beta$ 斑块引发过量钙(Ca^{2+})通过 NMDARs 内流进入神经元, 导致突触功能逐渐障碍和神经元细胞死亡[55]。在 AD 患者中 NMDAR 表达减少。研究表明, 应用 1Hz 低频 rTMS 可通过上调 NMDAR 的表达水平, 特别是提升海马区 NMDAR 的 NR1、NR2A 和 NR2B 亚基表达水平, 进而增强 LTP 效应及改善记忆功能。此外, 在 5 Hz rTMS 治疗后的血管性痴呆(VaD)大鼠模型中, 观察到 NMDAR 和 VEGF 表达增加[32], 1 Hz rTMS 治疗后也有此类作用[42]。Niimi 在 1Hz 低频 rTMS 治疗后也观察到 NMDAR 相关氨基酸的增加[56]。以上研究均证明 rTMS 可以通过调节神经递质和促进 NMDAR 的表达来改善认知症状。

2.6. rTMS 调节神经营养物质

神经营养因子(NTFs)参与调控神经元发育及功能活动, 如增殖、分化、迁移等[57], 其作用机制使其成为神经退行性疾病, 如阿尔茨海默病的重要研究靶点[58]。在 AD 中, 已经在不同的大脑区域中观察到 NTFs 的表达改变, 如神经生长因子(NGF)、脑源性神经营养因子(BDNF)、胶质细胞源性神经营养因子(GDNF)和睫状神经营养因子(CNTF) [59] [60]。大量实验研究表明受影响的大脑区域中的 NTFs 减少[58] [59]。AD 中神经营养因子的这些变化对神经退行性过程至关重要。神经营养因子的丢失可能是参与 AD 发病机制的一种机制[61]。因此, 神经营养因子的调节可能成为 AD 治疗的一个合适的治疗靶点。Choung 等[14]的一项研究表明, 20 Hz 高频 rTMS 可显著提升海马及皮层区域的 BDNF 水平。在许多其他研究中

也观察到 rTMS 治疗后 BDNF 的类似增加[62] [63]。BDNF 是一种神经营养素, 通过 BDNF-原肌球蛋白受体激酶 B (TrkB)信号通路发挥作用[60]。此外, rTMS 治疗正向调节 BDNF 受体 TrkB。例如, Chen 等研究观察到在 5 Hz HF-rTMS 治疗后 AD 脑中 TrkB 增加[63]。此外, LF-rTMS 也能调节 AD 中 NTFs 的含量。Tan 等研究报道了 LF-rTMS 对另一种 NTF NGF 的作用, NGF 是生长、发育、存活和神经元群体所必需的。与对照组相比, 1 Hz LF-rTMS 治疗上调 AD (注射 A β 的小鼠)组中的 NGF 含量[30]。以上研究均表明神经胶质细胞、星形胶质细胞及神经元释放的 BDNF 和 NGF 可通过 rTMS 干预增强表达, 进而促进记忆功能修复。Ma 等[64]进一步发现, 1 Hz 低频磁刺激可通过激活 BDNF/TrkB 信号轴, 触发 MAPK/ERK 与 PI3K/Akt 两条下游通路, 显著诱导神经元树突与轴突的形态学重塑, 我们推断低频磁刺激通过激活 BDNF-TrkB 信号通路参与调节海马神经元的结构性突触可塑性。但是, 目前评估 rTMS 治疗 AD 患者相关 BDNF 的精确机制并不完善, 仍需进一步探索。

2.7. rTMS 减轻神经炎症, 调节神经胶质细胞

当前研究已突破 AD 的传统神经中心论认知框架, 强调神经炎症在其病理进程中作为核心驱动因素的关键地位, 这一机制同样存在于其他神经退行性疾病中。临床流行病学调查发现超过 55 岁的非痴呆受试者应用非甾体抗炎药 2 年后患 AD 的风险可降低 80% [65]。因此, 抗炎对于预防或延缓 AD 的发病进展有一定的可靠性。促炎性细胞因子(如 TNF- α)通过跨膜受体介导的信号转导, 可激活 PI3K/Akt 等关键信号轴。该通路通过磷酸化级联反应调控 NF- κ B(核因子 κ B)的核转位效率, 促使后者与基因组特定应答元件结合, 驱动炎性介质(IL-6、TNF- α 等)的转录合成。这种正反馈式炎性信号扩增最终导致神经元微环境中炎性损伤级联反应的发生。陈虹茹团队等[66]采用 rTMS 协同电针治疗 AD 模型大鼠的研究表明, 该联合干预可显著下调海马区促炎因子 TNF- α 、IL-6 及 IL-1 β 水平。进一步分析表明, 其机制可能涉及抑制神经炎症级联反应、减轻突触结构损伤, 最终促进空间学习记忆与认知功能恢复。亦有研究表明, 长期 rTMS 可通过靶向调控 NF- κ B/STAT6 信号轴的双重机制发挥神经保护效应: 一方面抑制转录因子 NF- κ B 及 STAT6 的异常活化, 另一方面诱导小胶质细胞向抗炎表型(M2 型)极化。这种免疫微环境的重编程可协同抑制神经炎症病理进程, 同时通过减少神经元凋亡及促进突触可塑性实现神经功能重建[67]。董靖雯等[68]研究还发现 rTMS 减少了 AD 患者血清 TNF- α 、IL-6 的释放, 或许就是通过此通路减轻 AD 患者的炎症反应, 进而减少对突触的损害来提高患者的认知水平。Cha 等[69]采用高频 rTMS 刺激卒中后认知障碍(PSCI)患者患侧 DLPFC 区, 治疗 10 个疗程后患者血液样本中促炎因子 IL-1 β 、IL-6、转化生长因子- β 、TNF- α mRNA 水平显著下降, 且治疗 3 个月后 IL-1 β 仍维持在较低水平, 提示 rTMS 可持久减轻神经炎症。rTMS 的抗炎作用机制虽未完全阐明, 但现有证据表明其可通过靶向调控神经炎症微环境, 实现神经环路重构、海马长时程增强、记忆编码巩固及神经再生等神经重塑效应。这种多模态机制协同作用为 rTMS 干预神经退行性疾病提供了理论支撑。

2.8. 抑制氧化应激, 保护线粒体功能

氧化应激在 AD 的病因和发病机制中起着关键作用。细胞氧化还原状态、ROS 产生和受损的抗氧化剂防御的不平衡导致氧化应激[70]。AD 研究表明, 氧化应激和自由基损伤与 AD 的组织病理学特征有关, 如淀粉样斑块和神经原纤维缠结[71] [72]。细胞或神经元中 ROS(包括氧自由基超氧化物和过氧化氢)的过度积累导致 DNA 或 RNA 氧化损伤, 导致细胞死亡和组织损伤[74]。此外, 研究表明氧化应激和 BDNF 相互关联[73]。根据这一点, TMS 治疗非侵入性地调节和平衡 BDNF 和氧化应激水平, 从而在 AD 患者中发挥有益的抗氧化作用[74]。Velioglu 等[74]研究分析了将 20 Hz rTMS 应用于 AD 患者的外侧顶叶皮质, 在 20 Hz rTMS 处理后, BDNF 水平、总抗氧化状态、总硫醇水平和天然硫醇水平增加。氧化应激可

能是治疗神经退行性疾病的有效靶点;然而,在研究 TMS 对氧化应激、抗氧化防御系统、总氧化剂/抗氧化剂状态和抗氧化酶的影响方面,仍然存在很大的研究空白。未来需要更多的研究来填补这一研究空白。

2.9. rTMS 可促进脑血流量及代谢

大脑是人体能量代谢最丰富的器官。它在静息状态下即消耗机体约 20%的氧耗量和 25%的葡萄糖[75]。线粒体作为细胞能量代谢枢纽,其功能障碍与 AD 早期即出现的脑葡萄糖摄取及利用效率下降密切相关[76]。18F-FDG PET 成像技术作为评估脑能量代谢的金标准,可灵敏检测 AD 模型小鼠脑内葡萄糖代谢的细微异常[77]。临床研究证实,AD 患者脑葡萄糖代谢呈进行性衰减,其降低幅度与认知损害程度显著相关,且特定脑区代谢异常与对应功能域(如记忆、执行功能)障碍存在空间关联性[75]。Cao 等团队研究发现,rTMS 干预可显著提升 3xTg-AD 模型小鼠脑内 18F-FDG 摄取水平,提示其通过重塑脑能量代谢稳态,进而改善突触传递效能并促进认知功能恢复[78]。另外,Tremblay 等[79]研究则认为虽然高频和低频 rTMS 通常分别被认为是兴奋性和抑制性的,但这两种刺激类型都会导致局部血流量和代谢的增加,进而促进脑功能恢复。Cho 等[80]以 1 Hz 低频 rTMS 刺激健康受试者与认知及语言相关脑区,发现靶标区域受刺激后会促进糖代谢增加,提高靶标区域以及相互关联的语言、认知和情绪等相关脑区的兴奋性。这些研究表明,rTMS 可以通过提高脑血流量及脑代谢水平显著改善认知功能。

2.10. 调节大脑皮质兴奋性

通常来说,rTMS 是通过改变刺激频率来达到调节局部大脑皮层功能的目的,即低频脉冲(<1 Hz)会降低皮质兴奋性,高频脉冲(10~20 Hz)则会增加皮质兴奋性[81]。Ahmed 等[82]比较不同频率 rTMS 对 AD 患者认知功能的改善情况,研究结果显示高频 rTMS 干预组在简易精神状态检查(MMSE)等神经心理测评中展现出较低频组及假刺激组更优的临床改善,其作用机制可能与高频刺激增强目标脑区代谢活性、调控神经递质水平相关[83]。这可能也是高频 rTMS 治疗对 AD 患者有更好治疗效果的原因。但近期一项临床对照研究[84]发现,针对右侧 DLPFC 实施 1Hz 低频 rTMS 干预(2 周疗程),在治疗终止后 1 个月随访期内仍可维持识别记忆功能的持续改善,这提示不同频率刺激可能通过差异化神经可塑性机制产生治疗效果。rTMS 刺激治疗的频率选择尚未统一。因此未来尚需大量研究来阐明不同频率对 AD 患者的疗效差异及其神经影像学机制。

2.11. rTMS 调节神经网络震荡

γ 振荡在记忆等认知功能方面发挥着重要作用。在 AD 动物模型和 AD 患者中都观察到异常的 γ 振荡[85]。2018 年的一项研究,对 AD 动物模型进行 rTMS 治疗,研究发现 rTMS 改善了 $A\beta$ 大鼠的行为表现,增强了 γ 振荡,表明 rTMS 可以对抗 $A\beta$ 诱导的工作记忆以及 γ 振荡功能障碍,对工作记忆有潜在的改善作用[86]。Wang 等研究发现在 5xFAD 小鼠的海马穿通通路(PP)和齿状回(DG)区域的 θ 、 γ 振荡明显减弱。而在 rTMS 治疗之后,PP 和 DG 区域 θ 波段功率显著增加,在 DG 区域 γ 振荡在 rTMS 治疗后明显增强[87]。这些结果表明 rTMS 可能改善了 $A\beta$ 诱导的 γ 振荡功能障碍,从而对工作记忆产生潜在的益处。

3. rTMS 的安全有效性与不良反应

AD 的功能康复与病理逆转仍是神经科学领域的重大临床挑战。rTMS 作为非侵入性神经调控技术,具有安全性高、耐受性良好等特性,近年来被列为脑科学前沿技术。现有临床数据表明,rTMS 干预引发的副反应主要局限于短暂性头痛、局部不适或眩晕等自限性症状,而癫痫发作、尿潴留及听觉系统异常等罕见不良事件仅见于个案报道[88]。现有文献尚未见 rTMS 治疗导致致死性严重并发症的病例报道,鉴于此,该技术在临床实践中属于安全系数较高的非侵入性神经调控方法。

4. 展望

未来的研究应聚焦在以下方面: (1) 当前研究虽初步证实 rTMS 对 AD 的干预潜力, 但其神经调控机制仍存在多维度知识缺口。未来研究亟待通过动物模型构建及辅以电生理、影像学、遗传学、分子细胞生物学等相关技术, 为 AD 的精准神经调控提供理论依据。(2) rTMS 根据刺激参数如: 刺激位置、强度、持续时间、总脉冲以及刺激频率的不同, 干预的作用机制往往有所差异, 最终改善认知效果不同。故有必要深入探讨不同模式 rTMS 治疗 AD 的偏向作用机制, 为临床治疗不同病理改变诱发 AD 时 rTMS 的模式选择提供参考。(3) 结合神经功能影像学 and 遗传学研究进展, 探讨 rTMS 干预前后 AD 患者认知功能改善的脑网络影像, 筛选特征的影像学指标, 有可能为临床监测 rTMS 干预效果提供个体化的影像标志物。总之, rTMS 作为一种无创且安全性较高的非侵入性技术, 有可能在临床获得更加广泛的应用。

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