· 综 述 ·

阿尔茨海默病多模式非药物干预的研究进展

周颖[1]，李链[2] 综述；边国林[2] 审校

1.宁波大学医学部公共卫生学院，浙江 宁波 315211；2.宁波大学附属康宁医院，浙江 宁波 315201

摘要：阿尔茨海默病（AD）是以认知功能障碍和行为损害为特征的进行性神经退行性疾病，目前主要依靠药物治疗，但效果有限且伴随不良反应。多模式非药物干预（MNPI）是将2种或以上的非药物干预方式结合，协同改善AD患者的认知功能、精神行为症状、日常生活能力和生活质量，具有安全、经济和简便等优点。本文收集2018—2024年国内外发表的MNPI相关文献，对认知训练、体力活动联合其他干预方式的MNPI应用进行综述，为制定个性化AD干预方案提供参考。

关键词：阿尔茨海默病；多模式非药物干预；认知功能

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Multimodal non-pharmacological interventions for Alzheimer's disease: a review

ZHOU Ying[1], LI Lian[2], BIAN Guolin[2]

1.School of Public Health, Health Science Center, Ningbo University, Ningbo, Zhejiang 315211, China;

2.The Affiliated Kangning Hospital of Ningbo University, Ningbo, Zhejiang 315201, China

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive dysfunction and behavioral impairments. Currently, the treatment mainly relies on pharmacotherapy, yet its effectiveness is limited and accompanied by adverse reactions. Multimodal non-pharmacological interventions (MNPI), which combine two or more non-pharmacological intervention approaches, can synergistically improve cognitive function, neuropsychiatric symptoms, activities of daily living, and quality of life in AD patients, and offers advantages of safety, cost-effectiveness and simplicity. This article reviews MNPI-related literature published domestically and internationally from 2018 to 2024, and focuses on the application of cognitive training, physical activity, and other combined intervention methods in MNPI, providing the reference for developing personalized interventions for AD.

Keywords: Alzheimer's disease; multimodal non-pharmacological interventions; cognitive function

阿尔茨海默病（Alzheimer's disease，AD）是一种以认知功能障碍和行为损害为特征的进行性神经退行性疾病[1-2]。截至2019年，我国AD患者近1 000万例，且随着人口老龄化发展，预计患病例数会持续增长[3]。AD发病机制复杂[4-5]，目前主要依靠乙酰胆碱酯酶抑制剂和N-甲基-D-天冬氨酸受体拮抗剂等药物治疗，但临床疗效有限，长期药物治疗还会出现耐药性和不良反应[6]。非药物干预作为AD治疗的辅助手段，具有安全、经济和简便等优点，对患者认知、行为和生活质量的改善效果良好[7]。多模式非药物干预（multimodal non-pharmacological interventions，MNPI）是将2种或以上非药物干预方式结合，针对AD进行综合干预的策略，近年来受到广泛关注[8-9]。但AD患者的认知、精神行为症状和整体功能状态存在差异，可能影响MNPI效果[7]。本文通过PubMed、中国知网等数据库检索2018年1月—2024年1月有关MNPI的文献，对认知训练、体力活动联合其他干预方式的MNPI应用进行综述，为制定个性化AD干预方案提供参考。

1 认知训练联合干预

认知训练是一种通过结构化的训练任务，反复刺激与认知功能相关的特定脑功能分区（以下简称脑区），促进神经元连接，改善认知功能的干预方

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作者简介：周颖，硕士研究生在读，公共卫生专业

通信作者：边国林，E-mail：2584086@qq.com

法[10]。常见认知训练任务包括记忆力训练（如背诵词表）、注意力训练（如数字符号替代测验）和执行功能训练（如连线测验）等，通常采用难度递增的方式，每次20~40 min，每周3~5次，持续6~12周[11-12]。认知训练作为临床应用较为广泛的干预手段，可激活AD患者大脑中与记忆、注意和执行功能等认知领域相关的神经环路，有助于减缓病理性脑改变的进程[10]。然而，AD患者的认知损害涉及多个认知领域，单一认知训练的干预效果有限。近年来，研究者尝试在认知训练的基础上，辅以经颅磁刺激（transcranial magnetic stimulation，TMS）、虚拟现实（virtual reality，VR）等技术，多方面产生协同效应，更好地改善AD患者的认知功能。

1.1 认知训练联合TMS

TMS是一种无创的脑刺激技术，通过在头皮上施加磁场脉冲，诱导认知相关脑区产生电流，调控神经元活动[13]。重复经颅磁刺激（rTMS）根据刺激频率产生不同效应，在AD患者中，高频rTMS可兴奋认知相关脑区，增加突触可塑性；低频rTMS则可抑制异常过度激活的脑区，减少神经毒性作用[13-14]。

认知训练联合rTMS可有效调控认知功能相关脑区活动，促进受损认知功能恢复，其机制可能与特定脑区神经递质代谢改善有关。ZHANG等[15]利用随机对照试验探索认知训练联合高频rTMS（10 Hz）对AD患者认知功能和神经递质代谢的影响。实际rTMS组（刺激左侧背外侧前额叶或左侧颞上回）和伪rTMS组（在相同头皮位置放置线圈但不施加磁场刺激）均接受20 min/d的联合干预，持续4周后，实际rTMS组的AD评定量表认知部分（Alzheimer's Disease Assessment Scale-cog，ADAS-cog）得分均显著低于基线水平，且左侧背外侧前额叶的N-乙酰天冬氨酸/肌酸比率显著升高，该比率变化量与ADAS-cog变化量呈负相关。提示认知训练联合rTMS可改善AD患者认知功能。

认知训练联合rTMS对AD患者脑功能连接和精神行为症状也有积极影响。QIN等[16]利用静息态功能磁共振发现计算机化认知训练联合40 Hz rTMS（刺激双侧角回），每周3次，持续4周可增强AD患者灰质-白质功能连接强度并改善其工作记忆和语言流畅性。张漫等[17]比较了认知训练联合不同频率rTMS的疗效差异，结果显示，高频（10 Hz）、低频（1 Hz）rTMS组在干预12周和随访3个月时ADAS-cog、简易精神状态检查量表及神经精神问卷评分均优于对照组；进一步比较不同频率rTMS的效果发现，高频rTMS组在改善AD患者记忆、语言和整体认知功能方面优于低频rTMS组，但两组改善精神行为症状的效果相当。以上研究表明，认知训练联合rTMS可同时改善AD患者多个认知领域和精神行为症状，但不同频率刺激对脑区效应的差异仍需进一步探索。

1.2 认知训练联合VR

VR可创建高度沉浸式训练环境，通过身临其境的场景互动唤起患者的情感体验，提高其参与度[18]。VR任务可同时激活多个认知领域如注意、记忆和执行功能等[18-19]，有利于全面改善认知功能。此外，VR还可模拟日常生活情景，如购物、做饭等，促进训练获得的知识和技能在实际生活中得到应用[20]。因此，将VR与传统认知训练相结合，有助于从多感官、情景化等方面强化认知训练效果，为AD患者提供更个性化、更高效的治疗方案。

基于AD的研究进展，轻度认知障碍（mild cognitive impairment，MCI）会增加AD患病风险，对MCI患者早期进行认知训练，有助于延缓AD发生发展。一项有关MCI的随机对照试验发现，接受为期4周的VR认知训练（包括8个虚拟场景下的认知任务），MCI患者的视觉空间功能和日常生活能力较常规治疗组有明显改善[21]。另有研究发现，与常规认知训练比较，VR认知训练可提升定向力、视空间感知和反应速度等[18]。AD患者常伴有运动功能障碍，LIAO等[22]进一步将VR认知训练与体感游戏相结合，以兼顾认知与运动的双重治疗需求。30例MCI患者接受为期12周的VR游戏化认知运动训练，内容涵盖记忆、注意、执行功能和平衡等任务，与对照组比较，干预组在总体认知功能、双任务步态和平衡能力方面改善较明显，且焦虑、抑郁情绪也得到缓解。

综上所述，认知训练联合rTMS可调控特定认知脑区活动，促进受损认知恢复，同时改善脑功能连接和精神行为症状；认知训练联合VR则可提供沉浸式、针对性的训练，促进认知能力的迁移应用。认知训练联合rTMS目前已有一定的研究基础和机制探索，而认知训练联合VR的研究相对有限，未来还需更多研究证据支持其临床应用价值。

2 体力活动联合干预

研究表明，长期适量的体力活动与降低AD风险、延缓认知衰退相关[23]。体力活动可通过多种生物学机制，如增加脑血流灌注、促进神经营养因子分

泌、加强突触可塑性、减轻慢性炎症和氧化应激等，促进脑认知功能改善[24-25]。但仅通过体力活动干预AD效果有限。近年来，越来越多的研究将体力活动作为联合干预的基础，探索其与认知训练、营养干预和音乐治疗等协同应用的效果和机制。

2.1 体力活动联合认知训练

认知训练可直接刺激与认知功能相关的特定脑区[10]，体力活动可通过改善脑血流、促进神经递质分泌等途径，为大脑健康提供必要的生理基础[25]。2种干预方式联合可协同增强神经可塑性，促进认知功能改善。多项临床研究证实体力活动联合认知训练对MCI患者认知功能的积极影响。一项纳入69例MCI患者的随机对照研究比较了单独体力活动、单独认知训练、体力-认知联合干预和对照组的疗效差异，结果显示，体力-认知联合干预组改善总体认知功能、记忆力和躯体功能等指标的幅度优于其他3组，且效果可持续至干预结束6个月后[26]。一项针对MCI患者的有氧运动和记忆力训练联合干预研究发现了同样的结果，且干预组内侧颞叶萎缩速度慢于对照组[27]。

2.2 体力活动联合营养干预

既往研究表明，体力活动和营养干预可通过减轻慢性炎症、增强抗氧化防御系统[28-29]等机制，发挥神经保护作用。体力活动与营养干预相结合可通过多靶向机制，协同改善AD患者的认知功能，降低心血管疾病风险状况。一项关于有氧运动和抑制高血压饮食对MCI患者影响的研究表明，联合干预6个月后，在改善执行功能、语义记忆等认知表现及降低心血管疾病风险（总胆固醇、低密度脂蛋白胆固醇）方面，联合干预组优于单一干预组和对照组[30]。BLUMENTHAL等[31]在一项随访研究中也得出了类似的结论，有氧运动和抑制高血压饮食组在执行功能和临床痴呆评分量表得分优于健康教育对照组，且效果在干预结束1年后仍持续存在。

2.3 体力活动联合音乐干预

音乐干预是一种独特的非药物疗法，可通过节奏、旋律和歌词等同时激活大脑中与情感、记忆和注意力等认知功能相关的皮层下和皮层区域，改善患者总体认知功能[32]。体力活动与音乐干预相结合可在运动生理效应基础上，叠加音乐的神经调控作用，促进AD患者多个认知领域和身体素质改善。SHOKRI等[33]发现体力活动联合音乐干预（远程指导运动训练期间联合音乐认知刺激）对轻中度AD患者的定向力、记忆力、注意力和语言能力等认知功能及坐位体前屈等身体素质指标的改善效果优于单一体力活动干预组和对照组，提示联合干预能通过神经激活和唤醒，对改善患者的心理和身体产生协同效应。另一项研究对中度AD患者开展为期6周的音乐结合运动干预（音乐引导下的演奏、力量和平衡训练），与单一干预组比较，联合干预组AD患者的认知功能、注意力、即刻记忆、焦虑和抑郁情绪等改善更明显[34]，进一步支持了体力活动与音乐干预的协同效应。

体力活动与认知训练、营养干预、音乐干预等多种非药物干预方式联合应用，有望在改善脑血流灌注、减轻神经炎症等生理机制的基础上，协同促进AD患者认知功能和身体素质的改善，降低心血管疾病风险。大多数研究结果支持体力活动与其他干预方式联合应用可产生优于单一干预模式的效果，为AD的MNPI提供了依据。

3 小 结

MNPI通过综合运用认知训练、体力活动、TMS、VR、营养干预和音乐干预等多种干预方式，在认知功能、精神行为症状、日常生活能力和生活质量等方面发挥协同增效作用，是对传统药物治疗和单一非药物疗法的重要补充。然而，MNPI在AD中的应用仍面临挑战和不足。多数研究为初步探索性质，样本量偏小，证据有限；联合干预方案差异较大，效果评估指标也不尽相同，异质性明显；随访时间较短，长期效果尚不明确；针对不同严重程度、不同临床亚型的AD患者，缺乏个体化的联合干预方案。今后需开展大样本、高质量的随机对照试验，采用统一的疗效评价标准和随访时间，以判断不同联合干预方式对AD患者的持续性影响。同时，应深入探索联合干预的最佳组合模式、干预时机、频率和疗程等，针对AD患者实施个性化的联合干预方式。此外，应借助影像学、电生理和分子生物学等多学科技术手段，深入阐明联合干预的协同机制，为优化干预策略提供理论指导。

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