



电子、语音版

·综述·

计算机化认知训练干预糖尿病轻度认知障碍的研究进展

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摘要: 糖尿病(DM)是轻度认知障碍(MCI)和阿尔茨海默病(AD)的独立危险因素。中国≥60岁人群中 MCI 患病率为 14.5%, 每年 10%~15% 的 MCI 患者进展为 AD。糖尿病合并 MCI(DM-MCI)患者认知衰退更迅速, 目前尚无特效治疗药物。计算机化认知训练(CCT)因安全、经济、可居家实施, 成为延缓 MCI 向痴呆转化的潜在非药物干预策略。现有证据表明, 自适应、多认知域、持续至少 12 周的 CCT 方案可在短期内显著改善 MCI 患者整体认知功能和情景记忆, 其机制涉及海马默认网络功能连接增强、右侧角回灰质体积增加以及脑网络结构和功能耦合重塑。针对 DM-MCI 的探索性研究提示, CCT 可能通过提升执行功能间接优化糖尿病自我管理行为, 但对糖化血红蛋白等客观代谢指标的改善有限。然而, 当前证据存在明显不足。该综述系统地梳理了 CCT 干预 DM-MCI 的临床证据、神经机制及实施挑战, 为认知训练纳入糖尿病标准照护体系提供循证依据。

关键词: 轻度认知障碍; 糖尿病; 计算机化认知训练; 阿尔茨海默病

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Advances in computerised cognitive training for mild cognitive impairment in patients with diabetes mellitus

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Abstract: Diabetes mellitus (DM) is an independent risk factor for mild cognitive impairment (MCI) and Alzheimer disease (AD). In China, the prevalence of MCI among individuals aged ≥60 years is 14.5%, with 10%-15% of MCI patients progressing to AD annually. Patients with DM complicated by MCI (DM-MCI) experience more rapid cognitive decline, and no specific pharmacological therapy is currently available. Computerised cognitive training (CCT) has emerged as a promising non-pharmacological intervention strategy to delay the progression from MCI to dementia due to its safety, affordability, and feasibility for home-based delivery. Current evidence indicates that adaptive, multidomain CCT programs lasting at least 12 weeks can significantly improve global cognitive function and episodic memory in MCI patients in the short term. The underlying neural mechanisms involve enhanced functional connectivity between the hippocampus and the default mode network, increased gray matter volume in the right angular gyrus, and remodeling of structural and functional coupling across brain networks. Exploratory studies on DM-MCI suggest that CCT may indirectly improve diabetes

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self-management behaviors by enhancing executive function, but its effects on objective metabolic markers, such as glycated hemoglobin, are limited. However, obvious shortcomings exist in current evidence. This review systematically synthesizes the clinical evidence, neural mechanisms, and implementation challenges of CCT in DM-MCI, providing evidence-based support for integrating cognitive training into the standard care system for diabetes.

Keywords: mild cognitive impairment; diabetes mellitus; computerised cognitive training; Alzheimer disease

1 糖尿病与认知障碍

1.1 糖尿病与认知障碍的流行病学关联

随着人口的老齡化,阿尔茨海默病(Alzheimer disease, AD)的发病率逐年上升。一项针对中国人群的Meta分析显示,中国60岁及以上老年人口痴呆总患病率为6.0%,且随年龄增长上升:60~69岁为2.5%,70~79岁为6.1%,80岁及以上则高达17.0%^[1]。轻度认知障碍(mild cognitive impairment, MCI)是介于正常衰老与AD之间的过渡状态,特征为认知功能下降但日常生活功能基本完整^[2],通常被认为是AD最主要的临床前驱阶段,是延缓疾病进展而进行干预的关键窗口^[3-4]。

流行病学研究证实,2型糖尿病(type 2 diabetes mellitus, T2DM)是痴呆(尤其是AD)明确的独立危险因素^[5-6],且风险随年龄增长而上升^[7-8],已构成重大的公共卫生挑战。

1.2 糖尿病与认知障碍的病理生理机制

T2DM患者脑内的老年斑和神经原纤维缠结增加,与AD的发生相关^[9]。T2DM导致认知障碍的机制复杂,涉及胰岛素抵抗、慢性炎症、氧化应激以及线粒体功能障碍等多种通路^[10]。其中脑胰岛素抵抗被视为核心枢纽。T2DM状态下,外周及中枢的胰岛素信号通路受损,不仅导致脑内 β -淀粉样蛋白(amyloid β -protein, A β)清除障碍和tau蛋白过度磷酸化,直接加重AD特征性病理改变,还会引发下游级联反应。慢性高血糖通过促进晚期糖基化终末产物生成、诱发氧化应激与神经炎症,损害神经元与突触功能^[11-12]。糖尿病相关血管病变(如动脉硬化、脑白质病变)导致慢性脑低灌注,加剧神经元的缺血缺氧损伤^[13]。此外,反复发作的严重低血糖事件可直接损害海马等记忆关键脑区,并与认知下降形成恶性循环^[8, 14]。上述通路相互交织,共同驱动认知功能衰退。

1.3 MCI的可逆性及干预价值

中国 ≥ 60 岁人群中MCI患病率为14.5%^[15]。MCI具有高度动态性,既可逆转为认知正常,也可能进展为AD。Livingston等^[16]指出,控制可干预危险因素可预防或延缓40%的痴呆病例。每年有10%~15%的MCI患者进展为AD,该比例远高于认知正常的同龄人群,而即使“逆转”至认知正常的MCI患者,远期患痴呆风险仍显著升高^[17-18]。有证据表明,尤其在MCI早期,非药物干预(如

认知训练)能够有效改善认知功能,可能改变疾病进程^[19-20]。因此,开发针对MCI的有效干预策略具有重要公共卫生意义。

2 计算机化认知训练的理论基础与作用机制

2.1 计算机化认知训练的理论基础

计算机化认知训练(computerised cognitive training, CCT)是基于计算机技术的认知干预手段,通过强化特定认知能力(如记忆、注意力和执行功能),从而改善认知功能^[21]。CCT的核心优势在于通过标准化的任务设计确保干预的科学性和一致性,并利用自适应算法根据个体实时表现动态调整训练难度,维持最佳认知挑战水平^[22]。此外,CCT支持个性化定制,可脱离临床环境居家实施,显著提升干预的可及性^[20, 23]。上述特点使CCT具备了在MCI人群中推广应用的基本条件,以下将从神经可塑性、脑结构重塑及认知转移等层面阐述其作用机制。

2.2 CCT的作用机制

现有证据表明,CCT通过以下机制改善认知功能,即(1)增强神经可塑性:CCT可增强海马与默认网络(default mode network, DMN)的功能连接,改善认知相关脑区的活动水平^[24]。Kang等^[25]的随机对照试验(randomized controlled trial, RCT)发现,进行多认知域CCT 8周后,可改善MCI患者记忆功能,且与海马-额叶及梭状回-枕叶网络的功能连接增强相关。(2)促进脑结构可塑性:多认知域CCT可增加右侧角回灰质体积,延缓脑组织退化。Zhang等^[26]对遗忘型MCI患者进行6个月多认知域CCT干预,发现训练后右侧角回灰质体积显著增加,且该变化与词语学习记忆和视空间记忆评分呈正相关。(3)促进脑网络结构-功能耦合(structure-function coupling, SC-FC)的重塑:有研究采用静息态功能性磁共振成像(resting-state functional magnetic resonance imaging, rs-fMRI)和弥散张量成像技术,发现8周CCT可有效改善患者整体认知与记忆功能,且这些变化与DMN及躯体运动网络的结构-功能耦合增强和拓扑改变显著相关,提示CCT可能通过促进脑网络层面的结构-功能整合来发挥认知改善作用^[27-28]。(4)产生认知转移效应:CCT的获益不仅局限于训练所针对的认知域,还可迁移至其他未经训练的认知域^[25]。Kang等^[25]的研究证实,非记忆领域的多认知域CCT可产生向记忆领域的转移效应,拓展了CCT的认知

获益范围。

3 糖尿病合并MCI的CCT研究进展

3.1 CCT对认知功能的干预效果

一项针对中国MCI患者的RCT显示,6个月自适应CCT干预显著提升了患者的整体认知功能,训练组简易精神状态检查(Mini-Mental State Examination, MMSE)评分改善了0.23个标准差,而对照组则下降0.5个标准差。神经影像学分析显示,训练后双侧颞极、岛叶皮质及海马区域活动增加,提示CCT可能通过增强关键脑区间的功能整合来改善认知功能^[29]。然而,训练停止后疗效迅速衰减,提示维持和强化的重要性。这一发现与Silva等^[30]的研究结果一致。该研究显示,虽然推理和加工速度训练的效果可维持长达10年,但记忆训练的效果未能持续,而强化训练可产生额外且持久的改善。因此,未来的CCT方案应设计维持性训练阶段或定期强化训练,以巩固和延长训练效果。

近期发表的荟萃分析进一步支持了上述发现。Wei等^[31]纳入28项RCT、1 960例参与者,发现认知训练可显著改善老年MCI患者整体认知功能:蒙特利尔认知评估量表(Montreal Cognitive Assessment, MoCA)的均数差(mean difference, MD)为3.26;MMSE的MD为2.27。亚组分析显示,训练时长>6个月时效果更显著(MD=4.12)。Ye等^[32]的网络荟萃分析纳入28项研究、1 633例参与者,显示技术辅助的认知和运动干预在整体认知、加工速度、工作记忆和延迟回忆方面均优于对照组。以上研究主要聚焦于一般MCI人群。针对糖尿病合并轻度认知障碍(diabetes mellitus with mild cognitive impairment, DM-MCI)人群,An等^[33]的网络荟萃分析纳入25项研究、2 446例样本,显示认知训练是DM-MCI患者有效的非药物干预之一。

3.2 CCT对糖尿病自我管理的潜在作用

针对老年糖尿病患者的CCT研究发现,自适应CCT干预不仅改善了患者的认知功能,还显著提高了糖尿病自我管理能力(包括血糖监测、药物依从性及饮食控制等)^[34-35]。Bahar-Fuchs等^[34]的RCT显示,经过8周的多认知域CCT使自我报告的糖尿病照护评分得到改善,且效果可维持6个月。Silverman等^[35]在180例T2DM退伍军人群中的研究进一步证实,CCT干预6个月后,糖尿病自我管理显著改善,同时执行功能和前瞻性记忆也得到提升。这表明,CCT可能通过提升执行功能和决策能力,间接优化糖尿病管理。

Wang等^[36]的RCT纳入68例DM-MCI患者,随机分为12周分层支持模式互联网辅助自我管理治疗(stratified support pattern-based internet-assisted self-management

therapy, SISMT)组和对照组,结果显示,SISMT可改善空腹血糖、认知功能(MoCA、听觉词语学习测试、符号数字模式测试)、焦虑和生活质量,但对糖化血红蛋白(glycated hemoglobin A1c, HbA1c)和餐后血糖的影响,差异未达统计学意义。这提示,单纯认知训练或自我管理支持尚不足以全面优化血糖控制,需结合行为改变技术形成综合干预策略。

3.3 神经影像学证据支持

rs-fMRI研究显示,CCT干预后DMN功能连接呈现复杂变化;结构MRI则可观察到右侧角回灰质体积增加^[26, 37]。且该体积变化与词语学习记忆和视空间记忆评分呈正相关^[26]。一项78周的RCT显示,与填字游戏对照组相比,CCT组晚期MCI患者DMN内部功能连接下降,而对照组呈增加趋势;DMN与显著性网络间功能连接在CCT组减弱,对照组增强^[37]。

近年来的研究提供了更深入的机制阐释。Li等^[38]采用弥散张量成像和rs-fMRI发现,T2DM合并MCI患者在结构连接组中全局效率和局部效率显著下降;而在功能连接组中局部效率和聚类系数代偿性增加,提示功能可塑性是CCT的重要干预靶点。Kang等^[25]的RCT证实,CCT可增强海马-额叶和梭状回-枕叶网络功能连接,且与记忆改善相关。Wu等^[27]的RCT发现,CCT通过增强DMN和躯体运动网络的SC-FC改善认知功能。Hayashi等^[28]的综述系统总结了CCT对MCI患者生物标志物的影响,结果表明,CCT可引起包括DMN在内的主要脑网络结构和功能改变。这些结果进一步支持CCT通过促进脑结构可塑性和网络功能重组改善认知的观点。

4 CCT的依从性与实施挑战

居家CCT干预在实践中面临显著的依从性挑战。Bahar-Fuchs等^[34]报告,通用CCT条件下的依从性和保留率低于自适应CCT组,提示训练个体化程度直接影响患者参与度。Zhang等^[39]对19例老年MCI患者及4名家庭成员进行半结构化访谈,发现多数参与者未能完成标准剂量的CCT,脱落原因包括训练内容令人困惑、实际体验与预期不符、训练的“延迟满足”特性与患者“即时满足”需求冲突、经济负担及家庭压力等。该研究强调,持续使用行为不同于初始接受行为,会随使用体验动态演变。

此外,现有CCT研究多采用严格筛选的志愿者样本,外推性受限。有研究指出,愿意参与认知预防试验的志愿者往往是社交活跃、健康状况良好、教育水平较高,且认知功能较好的人群,这些特征可能降低研究结果的普适性^[40]。Silverman等^[35]的研究样本为特定退伍军人群体,其结果能否推广至普通社区DM-MCI人群尚待验证。T2DM合并认知障碍患者本身认知功能受损可能影响其

对训练方案的理解与坚持。虽然在一般MCI人群中已有研究表明,执行功能是预测CCT依从性的关键因素^[41],但这一结论在DM-MCI人群中的适用性仍需进一步验证,这间接提示该人群居家CCT的实施可能面临更大挑战。

5 小结与展望

5.1 主要发现

CCT作为非药物干预手段,在MCI人群中显示出一定的认知改善效果。现有证据表明,自适应、多认知域、足量(≥ 12 周)的CCT可中等程度改善MCI患者的整体认知功能、情景记忆和工作记忆,但对执行功能的疗效,各项研究的结果不一致。神经影像学显示,CCT可诱导脑可塑性改变,包括海马-DMN功能连接重塑、右侧角回灰质体积增加及SC-FC增强。针对DM-MCI人群的荟萃分析亦证实了认知训练的获益优势^[33]。

在此基础上,初步证据显示,CCT可能通过提升执行功能和决策能力间接优化糖尿病自我管理;但其对HbA_{1c}等客观指标的影响有限,提示单纯认知训练不足以全面优化血糖控制,需结合行为改变技术形成综合干预策略。

5.2 现有局限性

当前研究存在以下主要局限:第一,专门针对DM-MCI人群的CCT研究数量少、样本量小,缺乏血糖—认知双终点的综合评估设计;第二,随访时间普遍较短(多 ≤ 12 个月),CCT对痴呆转化率的长期影响尚不明确;第三,训练方案异质性大,自适应算法、训练剂量、认知域组合等关键参数的最优配置缺乏共识;第四,神经影像学机制研究尚处于探索阶段,神经可塑性变化与临床获益的因果关系有待验证;第五,居家CCT面临依从性下降、脱落率高等问题,现有研究多基于严格筛选的志愿者,外推性受限。

5.3 未来研究方向

未来研究应重点关注以下方面:开展多中心、大样本、长期随访的RCT,系统评估CCT对DM-MCI患者认知转归、痴呆转化率及血糖控制的综合影响;探索有效的维持强化方案(如间歇性强化训练、结合身体活动或社交互动),利用多模态神经影像技术深入解析CCT的神经机制,为个体化干预提供生物标志物;开发认知—行为整合干预方案,并验证其成本效益;开展基于社区的真实世界研究,探索提高居家CCT依从性的有效策略。

将认知管理纳入糖尿病标准化干预体系,对DM-MCI患者实施早发现、早诊断、早干预,是降低或延缓AD发病、减轻疾病负担的可行策略。优化CCT方案,建立认知—代谢双维度管理模式,有望提高患者生活质量和自理能力,具有重要的公共卫生意义。

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