

· 专家论坛 ·

轻度认知功能障碍的非药物干预——体育锻炼

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【摘要】轻度认知功能障碍(mild cognitive impairment, MCI)发生于阿尔茨海默病(Alzheimer disease, AD)的早期阶段,非药物干预手段是改善MCI患者认知功能的途径之一。在非药物干预方式中,体育锻炼正被越来越多人所关注。本文就体育锻炼对MCI患者认知功能改善做一综述,为MCI的治疗与管理提供思路。体育训练可分为有氧训练与阻力训练,两种训练方式均可以改善MCI患者的整体认知功能,但不同运动对不同认知领域的作用仍不明确。此外,体育训练联合其他非药物干预方式对MCI患者的认知功能改善也展现出一定潜力。另一方面,运动改善认知功能的机制与神经发生、神经元存活和突触可塑性有关,这既可以在分子细胞水平解读,也可以从器官等宏观角度分析。最后,本文指出进行同质性研究、运动处方的探索与远程运动管理的实施作为MCI与运动相关研究的可能方向。

【关键词】轻度认知功能障碍 阿尔茨海默病 体育锻炼 非药物干预 认知

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阿尔茨海默病(Alzheimer disease, AD)是导致痴呆的最常见原因,也是一个主要的公共健康问题^[1]。AD引起的轻

度认知功能障碍(mild cognitive impairment, MCI)发生在疾病的早期,此阶段存在明显的认知功能障碍迹象,但并不影响日常活动。尽管AD尚没有治愈的方法,但越来越多的证据表明,体育活动或许能够降低从MCI到痴呆的转换率^[2]。

体育锻炼旨在改善健康、提升生活质量。运动训练可以分成两种不同的类型:有氧训练和阻力训练^[3]。有氧锻炼可以提高有氧工作能力,进而增强心肺功能,减少脑血管疾病、运动障碍和残疾的发生^[4]。它包括很多常见的运动形

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式,如健步走、慢跑、水中有氧运动、游泳、跳舞和骑自行车^[5]。此外,当运动强度达到有氧供能系统的要求时,太极拳、瑜伽等几种特殊形式的运动也可归为有氧运动。另一方面,阻力训练通常被应用于从事运动相关工作的群体,或者其他想要诱导神经肌肉适应、以增加肌肉量和增强功能的个人^[6]。这些运动在本质上是无氧的,提供能量的燃料主要来自无氧糖酵解和三磷酸腺苷的分解。这种能量供应非常迅速,促进肌肉短时间内产生强力收缩^[7]。有氧代谢则随着运动持续时间的延长和强度的降低而增强。

1 运动锻炼与联合干预改善MCI患者的认知功能

有氧锻炼和阻力训练都能提高社区健康老年人的认知能力,并改善MCI患者的整体认知能力^[2,8-12]。然而,正向的结果与运动强度、持续时间和频率高度相关。例如,短时间、高频率的训练可能对认知改善有更大的效果,因为短时间的训练可能更不容易引起疲劳,这种情况与锻炼的能力和动机有关^[13]。另一方面,由于研究的异质性,运动对不同认知领域的作用也存在差异^[10,14]。

TALAR等^[14]在一项meta分析中得出结论,有氧运动对工作记忆和执行功能方面的影响没有统计学意义。与之对比,在一项临床试验中,有氧锻炼组和拉伸运动组的参与者进行每周4天、每次45~60 min的高强度活动,持续6个月。两组在多任务处理、认知灵活性、信息处理效率和选择性注意等执行控制过程中均取得较好的效果^[11]。此外,有证据表明,有氧运动提高了即时回忆和延迟回忆能力,但对意向、执行能力、语言流畅性或视觉空间功能等认知领域没有影响^[10]。

类似的,阻力训练可以提高MCI患者的执行功能和联想记忆能力^[8-9]。有趣的是,ZHU等^[15]发现进行等距握力练习对认知表现有长期的有益影响,但需要严谨的方法去评估练习的可行性和有效性。瑜伽是一种典型的有氧运动,它主要关注大脑、身体和精神之间的相互作用。EYRE等^[16]研究发现,昆达里尼瑜伽对记忆力改善的效果与认知训练类似,并且对执行功能和情绪症状具有额外的益处。此外,太极拳是中国传统体育运动之一,有证据表明,它可以改善老年MCI患者的总体认知表现、记忆、注意力、语言和执行功能^[17]。这些引起争议的发现表明,体育锻炼和认知之间存在复杂的关系。鉴于有氧运动的类型和(或)设置各不相同,对认知领域的确切影响需要未来更多科学的原始研究进一步明确。

从理论上讲,不同干预措施相结合可能会对MCI患者

认知功能提供更好的保护。事实上,有氧运动和认知训练的结合已经被证明可以减少视觉记忆和语言流畅性的衰退,并改善执行功能^[18]。一项meta分析还显示,认知-体育锻炼联合干预对MCI或痴呆老年人的整体认知功能具有积极的小到中等效应($SMD=0.32$ [0.17; 0.47], $P<0.00$),并且各研究之间无显著异质性^[19]。然而,不合适的干预组合可能效果不佳。例如,接受全训练量阻力训练和认知训练的患者在执行和总体认知方面的表现,明显较接受单独的渐进式阻力训练的患者差^[20]。这可能是由于联合干预会产生过大的压力,对精神和身体同时造成挑战,患者因此可能更少参与家庭或社区活动。另外,组合干预可能会导致副作用,抑制而非促进神经可塑性和认知效益^[20]。进一步来说,运动处方的提供和开具应该基于每例患者的具体情况,这将保证为每个人推荐合适强度的运动方式。

另一个有趣的研究方向是将体育锻炼与经颅直流电刺激(transcranial direct current stimulation, DCS)、经颅磁刺激(transcranial magnetic stimulation, TMS)或其他非侵入性手段结合来改善认知功能。尽管这一领域的相关文献有限,但新的证据表明,在改善认知相关的双任务步行方面,阳极tDCS联合太极训练效果优于假刺激联合太极训练^[21]。

目前正在进行的关于运动改善MCI患者认知功能的临床研究见表1。

2 运动改善MCI患者认知功能的机制

运动改善认知的内在机制尚未完全阐明。然而,运动诱导的大脑获益很大程度上与神经发生、神经元存活和突触可塑性有关。事实上,体育锻炼可能促进脑源性神经营养因子(brain derived neurotrophic factor, BDNF)等神经营养因子的产生、调节血清素和犬尿氨酸代谢、诱导肌脑交互作用中的肌细胞因子、增强抗炎反应和线粒体介导的调节作用^[22]。然而,一项meta分析的亚组分析证实,运动干预增加了MCI患者血清中BDNF水平,但趋势不显著($SMD=1.07$; 95%CI: -0.14~2.28; $I^2=86\%$; $P=0.080$)。产生这种不确定结果的原因可能是统计效力低,也可能是认知功能受损导致MCI患者按要求进行运动干预的能力降低^[23],这也是与个人运动处方计划相关的因素。另一个有趣的领域是线粒体和肌-脑轴的作用,BURTSCHER等^[24]证实,在体育锻炼后,骨骼肌中的线粒体会被激活,并分泌包括肌细胞因子、代谢产物和微小核糖核酸在内的循环因子,直接或间接地改善大脑线粒体健康,并可能使认知达到更好的状态。此外,有氧系统在决定长时间高强度运动的表现方面起着重要作用^[7]。

表1 正在进行的关于运动对 MCI 患者认知改善的临床研究

NCT 号	名称	疾病	干预	地区
NCT05540613	太极拳与常规运动对轻度认知障碍老年人认知功能的改善效果比较	MCI	1. 健康教育 2. 传统锻炼 3. 太极	中国香港
NCT02737878	通过改进运动处方重塑轻度认知障碍的路径	MCI	1. 有氧训练 2. 阻力训练 3. 平衡力量训练	加拿大
NCT03619577	运动和认知训练相结合对轻度认知障碍患者的有效性	MCI	认知训练联合有氧练习	中国台湾
NCT03855475	联合体育锻炼和认知训练对衰老大脑结构和记忆的有效性	MCI	1. 有氧练习 2. 拉伸	美国
NCT05310890	太极拳干预预防轻度认知障碍向痴呆转化的长期前瞻性研究	MCI	1. 太极训练 2. 团队活动	中国
NCT04070703	太极拳与老年轻度认知障碍患者认知功能的关系	MCI	1. 认知增强版太极运动 2. 标准太极拳	美国
NCT04185298	mSIM:移动同步有氧运动和记忆训练对遗忘型轻度认知功能障碍的干预	aMCI	1. mSIM 项目与运动监督 2. 运动监督	美国
NCT05663918	运动对轻度认知障碍个体和健康老年人突触可塑性的影响	MCI	自主强度间歇训练	加拿大
NCT02614365	基因、运动、神经认知与神经变性:基于社区的方法	MCI	1. 有氧练习 2. 拉伸练习	美国
NCT04997681	在家中同步进行步态和认知的锻炼、治疗	MCI	1. 有氧和阻力训练联合认知训练 2. 平衡力量训练联合认知训练	加拿大
NCT03313895	ACT 试验:有氧运动和认知训练联合治疗 MCI 的效果	MCI	1. 有氧练习联合认知训练 2. 骑行 3. 认知训练 4. 拉伸与精神刺激活动	美国
NCT04956549	通过运动-轻度认知障碍降低非裔美国人的阿尔茨海默病风险	MCI	体育锻炼项目	美国
NCT05370118	改善认知障碍患者的身体活动情况	MCI	远程康复身体活动行为干预	美国
NCT05030948	促进拉丁美洲老年人认知健康、心血管健康和睡眠的体育活动干预	MCI	步行练习	美国
NCT05375513	在家中同步进行锻炼和治疗改善认知	MCI	多领域干预	加拿大
NCT04689776	双重任务训练对认知功能下降老年人的有效性	MCI	双重任务训练	中国台湾
NCT05108246	面向老年人的以家庭为基础的双重任务训练	MCI	双重任务训练	美国
NCT05301868	轻度认知障碍的非面对面平台多领域干预	MCI	多领域干预	韩国
NCT05023057	通过面对面和视频交流平台对轻度认知障碍进行多领域干预	MCI	多领域干预	韩国
NCT04296565	增强退伍军人的记忆力:水上活动	MCI	水上活动联合认知训练	美国
NCT04507386	减少轻度认知障碍患者的久坐时间:为健康而站的研究	MCI	体育锻炼	巴西
NCT04059705	双重任务训练对 MCI 患者功能的影响	MCI	双重任务训练	美国

注:NCT,国家临床试验;MCI,轻度认知功能障碍;aMCI,遗忘型轻度认知功能障碍;mSIM,基于移动的同步运动和记忆技能训练计划;ACT,有氧练习联合认知训练。

过度活跃的有氧系统结合无氧糖酵解可能触发蛋白质的表达,这些蛋白将参与线粒体的产生和能量的生产,激活的有氧系统和糖酵解也会诱导氧化磷酸化相关蛋白的翻译,并促进骨骼肌中 ATP 的生成^[24]。此外,剧烈运动会引起循环干细胞和祖细胞数量的增加,并同时启动内源性神经干细胞的动员^[25-26]。这些分子或细胞通路可以直接促进海马神经元的活化和提高其可塑性,也可以通过增加脑血容量和毛细血管密度、改善全身情况等间接影响神经元^[22, 27]。有证

据表明,认知功能下降患者在接受体育训练后海马体积增大^[3]。

另一方面,β-淀粉样蛋白(β-amyloid, Aβ)斑块和细胞内神经纤维缠结的累积、tau 蛋白的过度磷酸化是 AD 的主要特征,并被认为是导致脑体积减小和脑功能下降的原因^[28]。来自动物研究的证据表明,运动可能有助于抑制 Aβ 产生和促进大脑中 Aβ 清除^[28]。同时,有证据表明,体育锻炼水平可能会影响大脑、脑脊液和人体血液中的 Aβ 水

平^[29]。LIANG等^[30]发现,达到美国心脏协会指导方针即7.5代谢当量小时/周运动的个体($n=69$),表现出明显较低的匹兹堡化合物B(Pittsburgh compound B, PiB,它是硫黄素T的类似物,是淀粉样蛋白成像最常用的示踪剂)结合水平和较高的脑脊液 $A\beta_{42}$ 水平,提示一种更健康的淀粉样蛋白谱。载脂蛋白E(apolipoprotein E, APOE) $\epsilon 4$ 等位基因是散发性AD最强的已知遗传危险因素^[31]。它与 $A\beta$ 聚集率升高、大脑 $A\beta$ 清除减少、认知能力下降和神经易损性增加有关^[28]。先前的研究表明,高水平体育活动可能会降低APOE $\epsilon 4$ 载体带来的 $A\beta$ 沉积风险的增加^[32]。此外,BROWN等^[33]证实,在报告最高体力活动水平且认知功能正常的老年人中,正电子发射扫描量化的tau蛋白水平较低。然而,随着关于 $A\beta$ 和tau的检测技术发展,我们希望有更多专门设计的、以运动为重点的随机对照研究,并把运用金标准测量的 $A\beta$ 和tau作为结果。此外,探明运动的神经保护机制也有助于药物的开发(图1)。

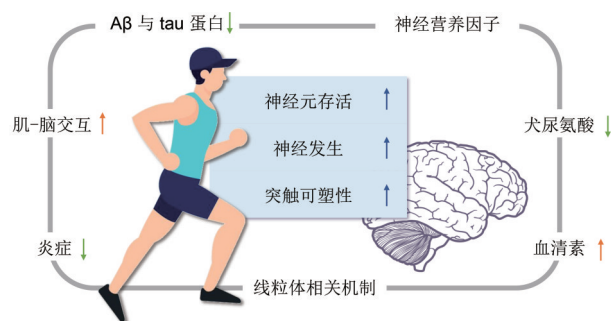


图1 运动改善MCI患者认知功能的可能分子和细胞机制 注: $A\beta$, β 淀粉样蛋白。

不同形式的体育锻炼可以通过作用于大脑不同区域来提高认知能力。据报道,有氧运动与海马的激活有关,而瑜伽则激活负责整合思想和情绪的额叶和岛叶。此外,举重通过对前额叶皮层作用来提高执行功能。在一项纵向研究中,对接受6周运动训练的年轻成人进行功能和结构MRI研究,结果显示额顶叶的网络连通性增加,并与认知功能的改善一致。灰质结构改变也与前额叶和辅助运动区的功能

连通性改变密切相关^[34]。此外,阻力训练已经被发现可以调节皮质脊髓的适应力和减少白质病变体积^[6]。总的来说,这些证据表明,一般性运动可能不能充分调动运动在MCI中的治疗潜力,包括内定模态网络、额顶网络和额叶执行网络等脑网络是认知衰退干预的潜在靶点^[35]。基于个体认知域损伤的精确运动处方是可取的,这可能需要同强度、持续时间和休息时间的锻炼计划,以最大限度地发挥运动对大脑健康的促进作用。

3 展望

远程锻炼指导或远程监督体育锻炼处于对抗认知衰退的新前线。MCI患者的短期运动干预通常在医院的健康中心进行,鉴于持续的运动可以提供长期保护作用,对MCI患者来说,长期的运动计划是必要的。然而,长期坚持有氧运动对MCI患者来说是一项挑战,因为这需要收集生理数据,并测量运动强度。新的文献表明,远程医疗是家庭认知训练的理想手段。在家锻炼可能是一个可行的选择,因为它方便时间安排,有良好的可接受性。在以家庭为基础的环境中,远程锻炼项目可以在家庭或附近社区的支持下,由专业教练提供远程监督,从而提高患者的依从性和提高锻炼的有效性。例如,Vivifrail项目是一个以家庭为基础的锻炼项目,其重点是根据老年人的功能能力制定个性化的多组分锻炼处方,经过12周的训练,试验组和对照组的认知功能和握力具有显著差异^[36]。另一方面,较低的握力已被发现与较高的全因痴呆发病率和死亡率相关,独立于重要的混杂因素^[37]。总之,握力可能是一种很有希望的评估体育锻炼效果的方法,也可能是认知能力下降的预测指标。综上所述,未来的研究需要考虑不同运动强度和运动时长的影响、运动/休息恢复比以及更合适的测量方法。此外,与单纯的步行、跑步或游泳相比,在运动中含有技巧元素的锻炼方式可能会带来更大的益处。

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Physical exercise: a promising non-pharmacological intervention for patients with mild cognitive impairment

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【Abstract】 Mild cognitive impairment (MCI) occurs in the early stage of Alzheimer disease (AD). Non-pharmacological interventions are one of the ways to improve the cognitive function of MCI patients. Among the non-pharmacological interventions, physical exercise is attracting more and more attention. This article reviews the effects of physical exercise on cognitive improvement in MCI patients, so as to provide ideas for the treatment and management of MCI. Physical training can be divided into aerobic training and resistance training. Both training methods can improve the overall cognitive function of MCI patients, but the effects of different exercises on different cognitive domains are still unclear. In addition, physical training combined with other non-pharmacological interventions also shows a certain potential for cognitive improvement in MCI patients. On the other hand, the mechanisms by which exercise improves cognition are related to neurogenesis, neuronal survival, and synaptic plasticity, which can be interpreted both at the molecular cellular level and from a macroscopic perspective such as organ. Finally, this paper provides conducting homogeneous research, exploration of exercise prescription and implementation of remote exercise management as possible directions for MCI and exercise related research.

【Key words】 Mild cognitive impairment Alzheimer disease Physical exercise Non-pharmacological intervention Cognition

1 Exercise and combined intervention can improve cognitive function in patients with MCI

Alzheimer disease (AD) is the most common cause of dementia and a major public health problem^[1]. Mild cognitive impairment (MCI) due to AD is a prodromal stage of AD where there are notable signs of cognitive impairment. However, MCI does not interfere with activities of daily life. Although there is no cure for AD, accumulated evidence suggests that physical activity may reduce the conversion rates from MCI to dementia^[2].

Exercise is a form of physical activity aimed to improve health and well-being. There are two distinct types of exercise

training: aerobic training and resistance training^[3]. Aerobic exercise can improve aerobic capacity, thereby enhancing cardiopulmonary capacity and reducing cerebrovascular disease, mobility limitations and disability^[4]. Aerobic exercise includes many commonly practiced exercises such as brisk walking, jogging, water aerobics, swimming, dancing, or bicycle riding^[5]. In addition, tai chi, yoga and several special forms of exercises can also be classified as aerobic exercise when the intensity of exercise meets the required demands of the aerobic energy supply system. On the other hand, resistance exercise is usually performed by athletic populations and individuals who would like to induce neuromuscular adaptations to increase muscle size and performance^[6]. These types of exercises are anaerobic in nature, and the fuel for energy provision comes predominantly from anaerobic glycolysis and the breakdown of adenosine triphosphate (ATP). The energy supply from these metabolic pathways is very rapid and facilitates strong powerful contractions over short time periods^[7]. Aerobic metabolism increases as the duration of the activity becomes longer and decreases in intensity occur.

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Both aerobic training and resistance training enhance cognitive performance in healthy, community-dwelling seniors and improve the overall cognitive performance of patients with MCI^[2, 8-12]. However, the positive outcomes are highly associated with intensity, duration and frequency of exercise. For example, shorter duration training sessions and higher frequencies may have greater cognitive effects in that short sessions may induce less fatigue, the condition associated with the ability and motivation to exercise^[13]. On the other hand, the action of exercise on the different domains of cognition remains diverse due to the heterogeneity of research^[10, 14].

In a meta-analysis, TALAR et al. concluded that there were no statistically significant effects of aerobic exercise on working memory and executive function^[14]. In contrast, in a clinical trial which participants in both the aerobic and stretching groups performed high-intensity activity routines 4 d/wk for 45 to 60 minutes per session for 6 months demonstrated favorable results. Both groups achieved a better executive control processes of multitasking, cognitive flexibility, information processing efficiency, and selective attention^[11]. Moreover, there is evidence that aerobic exercise improves immediate recall ability as well as delayed recall ability but not cognitive domain of intention, executive ability, verbal fluency or visuospatial function^[10].

Similarly, resistance training may promote executive function and associative memory in patients with MCI^[8-9]. Interestingly, ZHU et al. discovered a trend that implementation of isometric handgrip exercise has a beneficial chronic effect on cognitive performance, while the rigorous methodological approach is needed to evaluate the feasibility and effectiveness of the exercise^[15]. Yoga is a typical aerobic exercise with a focus on interactions among the brain, body and mind. Eyre's study found that Kundalini yoga had similar improvements on memory during cognitive training, with additional beneficial effects on executive functioning and mood symptoms^[16]. Additionally, Tai chi, as one of the traditional Chinese sports, showed evidence on improving cognitive performance, memory, attention, language and executive functions in older adults with MCI^[17]. The controversial findings suggest that there are complex relationships between physical exercise and cognition. Given that the types and/or settings of aerobic exercise vary

from one another, the precise effect on the cognition domains require more scientific original studies in the future.

Theoretically, the combination of different interventions may provide better protection on cognition in patients with MCI. Indeed, combinations of aerobic exercise and cognitive training, have been shown to reduce the decline of visual memory and verbal fluency and improve executive function^[18]. A meta-analysis also demonstrated a positive small-to-medium effect of combined cognitive-physical exercise interventions on global cognitive function in older adults with MCI or dementia ($SMD=0.32$ [0.17; 0.47], $P<0.00$), without significant heterogeneity across the studies^[19]. However, inadequate combinations may be less effective. For instance, patients receiving full doses of resistance training and cognitive training performed significantly poorer compared with isolated progressive resistance training on executive and global domains^[20]. This may be due to the excessive stress of the combined intervention, which was both mentally and physically challenging. As a result, patients may be less engaged with home or community-based activities. Alternatively, combinations may induce side effects that inhibit rather than promote neural plasticity and cognitive benefits^[20]. Further to this, the exercise training mode should be provided and prescribed to the patients on an individual basis. This will ensure that the modalities of exercise are prescribed at the correct intensities for individual subjects.

One interesting research direction would be to combine physical exercise with transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS), non-invasive tools to enhance cognition. Although the relevant literature in this area is limited, emerging evidence suggests that concurrent anodal tDCS and Taichi training was superior to a sham stimulation with Taichi training in improving cognitive dual-task walking^[21].

Ongoing clinical studies on exercise improving cognitive function in patients with MCI are shown in Table 1.

2 The mechanisms of exercise improving cognitive function in MCI patients

The underlying mechanisms have not yet been fully elucidated. However, exercise-induced brain benefits are largely

Table 1 Ongoing clinical studies of exercise on cognitive improvement in patients with MCI

NCT Number	Title	Conditions	Interventions	Locations
NCT05540613	Tai Chi Versus Conventional Exercise to Improve Cognitive Performance in Older Adults With Mild Cognitive Impairment	MCI	1. Health Education 2. Conventional Exercise 3. Tai Chi	Hong Kong, China
NCT02737878	Reshaping the Path of Mild Cognitive Impairment by Refining Exercise Prescription	MCI	1. Aerobic Training 2. Resistance Training 3. Balance and Tone Training	Canada
NCT03619577	The Effectiveness of Combining Physical Exercise and Cognitive Training for Individuals With Mild Cognitive Impairment	MCI	Cognitive training combining aerobic exercise	Taiwan, China
NCT03855475	Aging Brain Structure and Memory in Response to Exercise	MCI	1. Aerobic exercise 2. Stretching	United States
NCT05310890	Long Term Prospective Study of Tai Chi Intervention to Prevent MCI From Conversion to Dementia	MCI	1. Tai chi training 2. Group activity	China
NCT04070703	Tai Ji Quan and Cognitive Function in Older Adults With Mild Cognitive Impairment	MCI	1. Cognitive enhanced Tai Ji Quan 2. Tai Ji Quan	United States
NCT04185298	mSIM: Mobile Simultaneous Aerobic Exercise and Memory Training Intervention for Amnesic Mild Cognitive Impairment	Amnesic Mild Cognitive Impairment	1. mSIM intervention plus activity monitoring 2. Activity monitoring	United States
NCT05663918	The Effects of Exercise on Synaptic Plasticity in Individuals With Mild Cognitive Impairment and in Healthy Aging	MCI	Self-determined Intensity Interval Training	Canada
NCT02614365	Genes, Exercise, Neurocognitive and Neurodegeneration: Community-Based Approach	MCI	1. Aerobic exercise 2. Stretch exercise	United States
NCT04997681	SYNchronizing Exercises, Remedies in Gait and Cognition at Home	MCI	1. Combined Aerobic Exercise and Resistance Training with cognitive training 2. Balance and Toning Exercise Training with cognitive training	Canada
NCT03313895	The ACT Trial: Effects of Combined Aerobic Exercise and Cognitive Training in MCI	MCI	1. Aerobic exercise and Cognitive Training 2. Cycling Only 3. Cognitive Training Only 4. Stretching and Mental Stimulating Activities	United States
NCT04956549	Reducing African American's Alzheimer's Risk Through Exercise-Mild Cognitive Impairment (RAATE-MCI)	MCI	Physical activity program	United States
NCT05370118	Improving Physical Activity With Cognitive Impairment	MCI	Telerehabilitation physical activity behavioral (TPAB) intervention	United States
NCT05030948	A Physical Activity Intervention to Promote Cognitive Health, Cardiovascular Health and Sleep in Older Latinos	MCI	Tiempo Juntos Intervention	United States
NCT05375513	SYNchronizing, Exercises and Remedies to GaIn Cognition@Home	MCI	Muti-domain intervention	Canada
NCT04689776	The Effectiveness of Dual Task Training in Elderly With Cognitive Decline	MCI	Dual-Task Training	Taiwan, China
NCT05108246	Home-Based Dual-Task Training for Older Adults	MCI	Dual-Task Exercise Training	United States
NCT05301868	Multidomain Intervention Via a None-face-to-face Platform in Mild Cognitive Impairment	MCI	Multidomain intervention	Korea
NCT05023057	Multidomain Interventions Via Face-to-face and Video Communication Platforms in Mild Cognitive Impairment	MCI	Multidomain intervention	Korea
NCT04296565	Water-based Activity to Enhance Recall in Veterans	MCI	Water-based exercise + cognitive training	United States
NCT04507386	Reducing Sedentary Time in Patients With Mild Cognitive Impairment: The Take a STAND for Health Study	MCI	Physical activity	Brazil
NCT04059705	Dual-task Training for Function in MCI	MCI	Dual-Task Training	United States

related to neurogenesis, neuronal survival, and synaptic plasticity. Indeed, physical exercise may promote the production of neurotrophins such as brain-derived neurotrophic factor (BDNF), modulate serotonin and kynurenine metabolism, induce myokines in muscle-brain crosstalk, increase anti-inflammatory response and mitochondrial-mediated regulation^[22].

However, subgroup analyses of a meta study confirmed that exercise interventions increased plasma BDNF levels for MCI with a non-significant trend ($SMD=1.07$; 95% $CI: -0.14\sim 2.28$; $I^2=86\%$; $P=0.080$). The indeterminate result might be potentially due to low statistical power, but also to the reduced ability of MCI patients to comply with the prescribed exercise interventions because of their cognitive impairment^[23]. This is another factor related to individual exercise prescription regimes.

Another interesting field is the role of the mitochondria and the muscle-brain axis. BURTSCHER et al. demonstrated that mitochondria in the skeletal muscle will be activated after physical exercise and secreting circulating factors including myokines, metabolites and microRNAs, which directly and indirectly improve brain mitochondria health, possibly resulting in a better cognitive state^[24]. Moreover, the aerobic system plays a significant role in determining performance during high-intensity exercise over long exercise periods^[7]. An overactive aerobic system in combination with anaerobic glycolysis may be a trigger to upregulate proteins involved in mitochondrial biogenesis and energy production, to induce the translation of oxidative phosphorylation-linked proteins, and to improve ATP generation in skeletal muscle^[24].

Besides, acute exercise elicits an increase in circulating stem and progenitor cell numbers, while the mobilization of endogenous neural stem cells also begins^[25-26]. Together, these molecular or cellular pathways may directly increase hippocampal neuronal activation and plasticity in turn, or indirectly affect neurons through increases in cerebral blood volume capillary densities, as well as improvement in whole body situation^[22, 27]. Increased hippocampal volume has also been observed following physical training in people with cognition decline^[3].

On the other hand, beta-amyloid ($A\beta$) plaques and intracellular accumulation of neurofibrillary tangles, hyperphosphorylated tau proteins, are the primary hallmarks of AD, and are proposed to contribute to a decline in brain volume and function^[28]. Comprising evidence from animal studies suggests that exercise may contribute to both the inhibition of $A\beta$ production and enhancement of $A\beta$ clearance in the brain^[28]. Meanwhile, there is evidence that physical exercise levels might affect $A\beta$ levels in the brain, cerebrospinal fluid (CSF), and blood in human bodies^[29]. LIANG et al. found that individuals ($n=69$) meeting the American Heart Association guidelines of 7.5 metabolic equivalent (MET) hours/week of exercise showed significantly lower PiB (The Pittsburgh compound B, which is the analogue of thioflavin T, is the most commonly used tracer for amyloid imaging) binding and higher levels of $A\beta_{42}$ in the CSF, indicating a healthier amyloid profile^[30]. The Apolipoprotein E (APOE) $\epsilon 4$ allele is the strongest known genetic risk factor for sporadic onset AD^[31]. It is associated with higher rates of $A\beta$ aggregation, reduced clearance of $A\beta$ from the brain, increased rate of cognitive decline and neuronal vulnerability^[28]. Previous research suggested higher levels of physical activities may lead to mitigating the increased risk of $A\beta$ deposition conferred by APOE $\epsilon 4$ carriage^[32]. Besides, BROWN et al. demonstrated lower levels of PET-quantified tau in cognitively normal older adults reporting the highest levels of physical activity^[33]. However, as the measurements of $A\beta$ and tau are developing, studies applying gold-standard tau and $A\beta$ measurements as outcome measures in specifically designed exercise-focused randomized controlled trials are expected. Furthermore, identification neuroprotective mechanism by exercise may also contribute to drug development (Figure 1).

Different forms of physical exercise may improve cognitive ability by targeting different areas of the brain. Aerobic exer-

Figure 1 Possible molecular and cellular mechanisms of exercise improving cognitive function in MCI patients

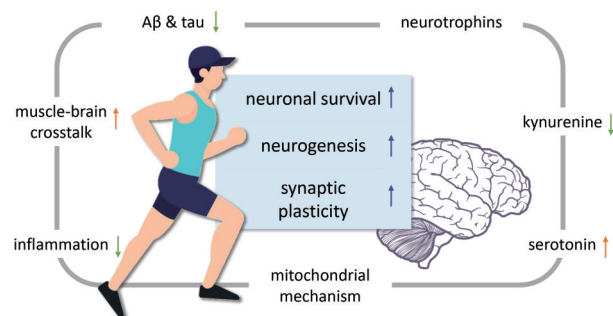


Figure 1 Possible molecular and cellular mechanisms of exercise improving cognitive function in MCI patients

cise has been reported to be associated with the activation of the hippocampus, while Yoga activates the frontal lobe and insula, which are responsible for integrating thoughts and emotions. In addition, lifting weights boosts executive function through the action on the prefrontal cortex. Longitudinal functional and structural MRI study of young adults who accepted a 6-week motor training showed increased fronto-parietal network connectivity in accordance with cognitive performance improvements. The structural gray matter alterations were also tightly correlated with functional connectivity changes in prefrontal and supplementary-motor areas^[34]. Moreover, resistance training has been found to modulate corticospinal adaptations and lower white matter lesion volume^[6]. Collectively, this evidence suggests that generic exercise may not take full advantage of therapeutic potential of exercise in MCI. Several brain networks including Default Mode Network mainly, Fronto-Parietal Network and Fronto-Executive Network are potential targets for the interventions of cognitive decline^[35]. Precision exercise prescription based on individual cognitive domain impairment is desirable. This may require exercise regimes of different intensities, durations and rest recovery periods to maximize the full benefits of exercise on brain health.

3 Expectations

Tele-exercise or remoted-supervised physical exercise is a new frontline in the battle against cognitive decline. Short-term exercise interventions in MCI people were usually conducted in hospitals health centers. Given that sustainable exercise can provide long-term protective effects, a long-term exercise program is necessary for MCI patients. However, long-term adherence to aerobic exercise is challenging for patients with MCI in that the physiological data needs to be collected and needs to be measured for the establishment of exercise intensity. Home-based Emerging literature has demonstrated that telemedicine is an ideal tool for home-based cognitive training. Home-based exercise may be a feasible option because of its convenient schedule and easy acceptability. In the home-based setting, tele-exercise programs can provide remote supervision by professional trainers while being supported by the family or near communities, thus improving patient adherence and increasing effectiveness of exercise. For

instance, the Vivifrail programme was a home-based exercise programme focused on individualized multicomponent exercise prescription according to the functional capacity of the older adults. After 12 weeks of training, significant differences were observed for cognitive function and handgrip strength^[36]. On the other hand, lower handgrip strength has been found to be associated with a higher risk of all-cause dementia incidence and mortality, independent of important confounding factors^[37]. Together, handgrip strength may be a promising measurement for the effect of physical exercise as well as a predictor for cognitive decline. In conclusion, future research needs to consider the effects of different intensities of exercise, the effects of different durations, work to rest recovery ratios and more suitable measurements. Further to this, exercise modalities that have an element of skill in the exercise being performed may provide greater benefits than simply walking, running or swimming.

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