

基于静息态功能磁共振成像技术 观察 rTMS 对轻度认知障碍患者 认知功能改善的可行性思考

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摘 要: 近年来, 临床症状尚轻微的轻度认知障碍成为认知研究中的焦点, 临床证明早期的识别和干预对轻度认知障碍的预后至关重要。本文旨在综述轻度认知障碍的现状与静息态功能磁共振成像技术与重复经颅磁刺激对轻度认知障碍的相关研究, 探索静息态功能磁共振成像技术观察重复经颅磁刺激对轻度认知障碍认知功能改善的可行性, 通过大脑功能网络的改变来为研究中治疗方法的疗效提供理论依据, 指导临床轻度认知障碍患者认知功能的改善。

关键词: 轻度认知障碍; 重复经颅磁刺激; 静息态功能磁共振成像技术; 可行性

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Feasibility of observing rTMS on improving the cognitive function of mild cognitive impairment based on resting state functional magnetic resonance imaging

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Abstract: In recent years, mild cognitive impairment with mild clinical symptoms has become the focus of cognitive research. It has been clinically proven that early recognition and intervention are essential for the prognosis of mild cognitive impairment. This article aims to review the current status of mild cognitive impairment and the related research of resting-state functional magnetic resonance imaging and repetitive transcranial magnetic stimulation on mild cognitive impairment. The feasibility of improving cognitive function of cognitive impairment, through the change of the brain function network, to provide a theoretical basis for the efficacy of the treatment method in the study, and to guide the improvement of cognitive function in patients with clinically mild cognitive impairment.

Key words: mild cognitive impairment; repetitive transcranial magnetic stimulation; resting state functional magnetic resonance imaging; feasibility

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1 引言

阿尔茨海默病 (Alzheimer's disease, AD) 是老年痴呆中最常见的一种进行性中枢神经系统退行性疾病, 95% 以上属于晚发型 AD [1]。随着社会人口老龄化的发展, AD 发病率逐年递增。研究显示, 全世界有超过三千五百万的 AD 患者, 65 岁以上人群年龄每增加 5 岁, 患病率将增加一倍, 80 岁以上老年人 AD 患病率高达 20% [2]。预计到 2050 年, 全世界将有超过 1 亿的 AD 患者 [3]。中国 60 岁及以上人群的老年痴呆患病率已经达到 4.2%, 65 岁及以上人群患病率达到 5.9%, 接近发达国家水平 [4]。2013 年 9 月国家卫生和计划生育委员会和全国老龄工作办公室联合发布了《中国老年人健康指南》, 指南强调中国已经进入人口老龄化快速发展期, 2013 年底老年人口已达到 2.02 亿, 失能半失能达到 3750 万, 未来 30 年老年人口还将继续增多, 老年健康问题将愈发突出 [5]。据全球疾病负担研究组 (Global Burden of Disease Study, GBD, 2010) 报道, 近 20 年来 AD 的病死率上升了 2 倍 [6]。美国的数据也表明: 2000 年到 2008 年 AD 病死率上升了 66% [7]。我国目前老年人群 AD 患者人口约 1000 万, 预计到 2050 年将超过 2000 万, 未来几十年我国将面临着 AD 相关的巨大社会和经济负担 [8]。由于 AD 的临床诊断多数在中晚期, 此时的治疗效果不佳, 因而研究的注意力开始转向 AD 的早期诊断和早期干预, 即轻度认知障碍 (mild cognitive impairment, MCI) 成为近年的研究热点 [9]。本文就重复经颅磁刺激 (repetitive Transcranial Magnetic Stimulation, rTMS) 对 MCI 患者进行治疗, 并采用无创的静息态功能磁共振成像技术 (resting-state functional magnetic resonance imaging, rs-

fMRI) 来观察 MCI 患者的大脑功能活动相关研究进行综述, 以期为未来临床研究提供理论依据。

2 MCI 研究现状

老年人一旦发展到 AD 阶段, 就很难逆转, 目前对 AD 的研究逐渐趋向 AD 前期阶段——轻度认知障碍或者轻度神经认知障碍 (mild neurocognitive disorders)。MCI 是从认知正常到痴呆的一个中间阶段, 患者表现出与自身年龄和受教育程度不相符的认知功能损害, 但日常生活能力基本保留, 达不到现有痴呆的诊断标准 [6]。研究表明, 每年有 10% ~ 15% 的 MCI 患者进展为痴呆, 而健康老年人每年仅有 1% ~ 3% 进展为 AD [10]。MCI 发展为痴呆的主要记忆功能改变有定向、识记、视觉、触学等短期记忆显著下降 [11], 定向记忆的显著下降作为预测痴呆的因素, 有助于痴呆的早期识别和预防 [12]。MCI 是一个临床综合征, 病因学上具有异质性, 很多引起痴呆的病因都可能是 MCI 的潜在病因 [13]。根据认知损害的特征可以将 MCI 分为不同的类型, 根据是否存在以记忆损害为主, 将 MCI 分为遗忘型和非遗忘型; 根据损害是单区域或多区域进一步细分为单区域型和多区域型 [14]。随着病情加重, 患者逐渐出现认知和日常生活能力进一步下降, 依赖他人照料, 转化为痴呆 [15]。因此, MCI 的早期筛查和干预对延缓痴呆的发生和发展至关重要。不过由于 MCI 的病理生理学机制尚不明了, 诊断方法和标准尚不统一, 因此 MCI 患者并不能得到及时而准确的诊断, 从而丧失了早期干预的机会。

3 rTMS 改善 MCI 患者认知功能

多项临床研究表明 rTMS 可改善 MCI 患者的认知功能, 提高患者的自我生活能力 [16], 最新研究显示 rTMS 能够改善遗忘型 MCI 患者认知功能 [17], 并且能够改善患者冷漠情感 [18]。rTMS 是一种无创的可以直接影响相应受刺激部位皮质兴奋性变化的一种刺激技术 [19], 具有非侵入性、无痛、无创、安全性高等特点, 并通过将电磁脉冲信号透过颅骨传送到大脑皮层, 刺激特定脑区的神经以达到治疗效果 [20]。研究发现, MCI 患者存在明显的双侧扣带

回 / 楔前叶区功能连接下降、双侧前额皮质及左侧海马区功能连接增加 [21]。rTMS 通过改变神经元轴突的可塑性和重建来调节皮质回路和神经元的兴奋性 [22]，rTMS 治疗后 MCI 患者表现出皮质过度兴奋且突触可塑性在改变 [23]。Drumond 等 [24] 对 MCI 患者每天进行 rTMS 治疗，连续治疗 10 天后，利用行为记忆测验法进行认知功能评估，结果发现患者的日常记忆明显改善，且效果持续 1 个月。Padulles 等 [25] 对 40 位 50 岁以上的伴有记忆下降的老年人予以高频 rTMS (5HZ, 80% 运动阈值) 刺激，利用 rs-fMRI 和面孔命名任务作为评估指标，结果发现真刺激组的准确率明显提高，并伴有右侧背外侧前额叶的激活增强。Eliasova 等 [14] 对 AD 患者或 MCI 患者进行右侧额下回予以 rTMS 刺激，以连线测试为疗效指标，结果发现治疗后患者的测试结果明显改善。此外，rTMS 除了对神经元的功能产生影响，还可增加脑血流从而促进神经再生和神经轴突的形成 [26]。

4 rs-fMRI 探索 MCI 病理生理机制

近年来，神经影像学技术的发展为探索 MCI 的病理生理机制提供了新途径，rs-fMRI 是近年来应用于脑科学研究的一项功能影像学技术，随着 rs-fMRI 在神经科学尤其在认知神经领域的迅速发展和应用，可能为揭示 MCI 的脑神经病理生理损害机制提供新的视角 [27]。功能磁共振成像功能十分强大，能够检测 MCI 治疗过程中的细微变化 [28]，研究发现，MCI 患者的海马和内嗅皮质的体积减少，处于 AD 和正常老化之间，且减少的速度要快于正常老化人群，而这种体积减少可提示患者正由 MCI 向 AD 转归 [29]。后续研究使用 voxel-based 形态测量学测量磁共振成像上的 MCI 患者序列发现，海马、杏仁核、颞叶、额叶灰质体积减少横贯整个病程（从 MCI 到 AD） [30]。约 70% MCI 患者显示磁共振成像异常，1/3 以上与血管病有关，1/5 有弥漫性脑萎缩，1/6 有内侧颞叶萎缩 [31]。静息状态是指受试者保持清醒的休息状态、闭眼、放松并避免任何有结构的思维活动状态。rs-fMRI 研究内容包括脑局部自发运动、脑区功能连接和脑网络分析三个层面，可结合多种数据分析方法，例如局部一致性 (regional homogeneity, ReHo)、低频震荡振幅 (amplitude of low-frequency fluctuation,

ALFF)、独立成分分析(independent component analysis, ICA)和选取种子点分析等[32],来探究大脑在静息状态下的局部或全脑活动状态并对脑网络特征进行观察。同时探查大脑所有网络及其内在关系,且更加简单、方便、容易操作,尤其适用于不能配合执行任务的儿童和认知损害者[33]。Parra MA 等利用 rs-fMRI 对 35 例 MCI 患者进行了内侧颞叶区的一项前瞻性研究显示,在临床痴呆量表评估中损害较重的患者,其右侧海马旁回的启动程度较高;并指出这种启动程度的增高可能是病理蓄积的反应,可以将其作为临床症状进展的一个重要标志[34]。有研究显示[35],与正常老人相比,AD 患者在执行认知任务时,额叶、颞叶、顶叶等脑区出现激活,这种变化可能与代偿性或资源重新分配有关。其中,小脑后叶、丘脑及尾状核连接的升高可能通过增强相关认知功能网络来弥补 AD 患者的默认网络功能的下降。He 等[36]基于图论的脑网络分析技术研究认为,MCI 和健康对照组都具有较高节点强度的脑区空间分布上高度一致,且顶叶后部和枕叶皮层均显示较高节点强度,说明两组具有相类似的核心脑区(主要分布在大脑的联络皮层区域和边缘系统)分布模式,但 MCI 患者的核心脑区的功能连接强度普遍降低。rTMS 能够改善精神障碍患者认知功能障碍,并且 rs-fMRI 可以检测出治疗过程中生物标志物的变化[37],基于此我们预测 rs-fMRI 技术观察 rTMS 对 MCI 患者认知功能改善是可行的。

5 展望

老年人认知问题已成为全球性公共卫生问题,临床症状尚轻微的 MCI 是认知研究的焦点,早期的识别和干预对 MCI 的预后至关重要。rs-fMRI 是研究脑认知科学的利器,利用 rs-fMRI 可观察到治疗方法对认知功能的中枢性作用机制。未来研究可以考虑基于 rs-fMRI 技术观察 rTMS 对 MCI 患者脑功能的影响,探讨其对认知功能的中枢作用机制,为临床应用提供理论依据。采用基于独立成分分析的方法对 MCI 患者的全脑网络及网络内功能连接进行分析,以期在无先验假设的情况下,客观而全面地反映 MCI 患者 rTMS 治疗前后静息态脑网络的变化,探讨 rTMS 对 MCI 患者认知功能康复的影响。

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