·综述·

抑郁障碍的重复经颅磁刺激疗效预测生物标志物研究进展

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【摘要】 重复经颅磁刺激(rTMS)是常用的治疗抑郁障碍的非侵入性神经调控方法。无效的rTMS治疗给抑郁障碍患者带来了极大的经济和心理负担，因此迫切需要可靠的临床疗效预测生物标志物。现对rTMS治疗抑郁障碍的电生理及影像疗效预测生物标志物进行归纳总结与讨论，以为指导抑郁障碍治疗的临床实践提供理论支持。

【关键词】 抑郁障碍； 重复经颅磁刺激； 影像； 电生理； 生物标志物； 综述
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Research progress on biomarkers for predicting the efficacy of repetitive transcranial magnetic stimulation in depressive disorders

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【Abstract】 Repetitive transcranial magnetic stimulation (rTMS) is a widely used non-invasive neuromodulation method for the treatment of depressive disorders. Ineffective rTMS imposes significant financial

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and psychological burdens on patients with depressive disorders, hence the urgent need for reliable predictive biomarkers to predict clinical efficacy. This paper summarizes and discusses the electrophysiological and imaging biomarkers for predicting the efficacy of rTMS for depressive disorders, aiming to provide theoretical support to guide clinical practice in the treatment of depressive disorders.

【Key words】 Depressive disorder; Repetitive transcranial magnetic stimulation; Imaging; Electrophysiology; Biomarkers; Review

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抑郁障碍是一种常见的心境障碍，已成为精神疾病负担的最主要原因[1]。约有1/3的抑郁障碍患者对药物治疗无效[2]，亟须新的治疗手段。rTMS作为一种非侵入性神经调控技术，已被广泛应用于抑郁障碍的临床治疗，但其治疗效果存在显著异质性[3]。无效的rTMS治疗为抑郁障碍患者带来了沉重的经济与心理负担，因此寻找有效的rTMS疗效预测生物标志物以实现个体化和精准治疗尤为重要。现就抑郁障碍rTMS疗效预测生物标志物进行归纳总结与讨论，旨在为抑郁障碍的个体化治疗提供理论支持。

一、rTMS概述

rTMS通过发出磁脉冲直接刺激大脑中参与情绪控制、与抑郁相关脑区的神经细胞，激活或抑制特定脑区的神经元活动，从而对神经元网络进行调控[4]。除常规的rTMS外，间歇性θ脉冲刺激(intermittent theta burst stimulation, iTBS)可模拟内源性θ节律，是一种特殊的rTMS模式，已被证实拥有不劣于传统10 Hz rTMS的抗抑郁疗效[5]。rTMS治疗最常见的刺激靶点为背外侧前额叶(dorsolateral prefrontal cortex, DLPFC)，近年来亚属扣带回皮层(subgenual anterior cingulate cortex, sgACC)相关靶点也是学者们关注的热点[6]；此外，靶向眶额叶皮层[7]、视觉皮层[8]及腹内侧前额叶(ventromedial prefrontal cortex, vmPFC)[9]等的rTMS治疗也被发现对抑郁障碍有效。但传统的以DLPFC为靶点的rTMS治疗效果不一，而新靶点在人群中的疗效缺乏稳健有力的证据。因此，识别可量化、稳定的疗效预测生物标志物对于优化靶点选择、实现精准神经调控及提升治疗应答率具有关键意义。

二、神经电生理标志物

抑郁障碍患者往往在特定脑电频段显示出显著的活动差异，如额叶α不对称性、慢波活动的增强(δ、θ)、静息状态下相对较高的β和γ功率。抑郁障碍患者诱发电位相关成分也存在异常。研究表明，抑郁障碍患者脑诱发电位中，P300和N400潜伏期延长，P300波幅度降低，且降低程度与抑郁症状严重程度相关。此外，视觉、听觉、体感诱发电位的振幅与潜伏期也存在异常[10]。rTMS可通过电磁感应在大脑中产生微弱的电流改变大脑的电生理活动，从而改善抑郁症状，且rTMS治疗前后的脑电特异性变化与rTMS疗效高度相关。

(一)静息态脑电图

1.α频段：α波(8～13 Hz)主要分布于感觉运动皮层、视觉皮层及枕叶区域，其振荡活动与注意力调控、意识状态及高级认知功能密切相关[11-12]。α振荡可通过调节GABA能中间神经元活性维持皮层兴奋-抑制平衡，低α功率可能反映抑制功能不足[13-14]。临床研究表明，静息态α功率降低可能预示rTMS疗效更佳。Woźniak-Kwaśniewska等[15]的小样本开放标签研究(n=18)发现，10 Hz rTMS治疗有效的抑郁障碍患者的额叶α功率显著低于无效者，可能与高频刺激选择性激活GABA能神经元、增强局部抑制功能有关。Zandvakili等[16]的脑电连通性分析发现，静息态α相干性在共病创伤后应激障碍的抑郁患者中可作为rTMS疗效预测指标。此外，个体α峰值频率(individual alpha frequency, iAF)，即个体在安静状态下脑电活动中α波的主要频率与rTMS治疗的临床效果密切相关。Voetterl等[17]在接受10 Hz或1 Hz rTMS治疗的患者(n=196)中发现，iAF接近10 Hz时，接受10 Hz rTMS治疗的患者的缓解率更高，而iAF较高时，1 Hz rTMS的效果更为显著，盲法验证进一步证实了此发现。

2.β频段：β波(13～30 Hz)一般在额叶和中央区域最为显著，与注意力、运动控制[18]和情绪调节[19]等大脑功能密切相关[20]。多项研究探讨了β波在rTMS治疗抑郁症中的预测价值。在一项纳入28例难治性抑郁症的试验中，Kavanaugh等[21]聚焦于抑郁障碍患者的认知功能障碍，发现5 Hz或10 Hz rTMS治疗前的额叶与顶叶的β事件发生率可预测治疗对抑郁障碍患者执行功能的改善，较低的β事件发生率与执行功能改善相关，且β频段

相较于其他频段具有特异性，表明β事件与刺激评价和决策等高级认知活动相关。Hasanzadeh等[22]的研究亦支持这一发现，rTMS治疗前较高的β波功率可能与rTMS治疗效果欠佳相关。Zandvakili等[16]在抑郁障碍共病创伤后应激障碍患者中也得出了相似的结论。

3. θ频段：θ波(4～8 Hz)主要分布于额中线(Fz)，与海马-前额叶环路功能密切相关[23]。Baily等[24]对50例难治性抑郁症患者和20名健康对照进行了基线和1周的脑电采集，经过6～8周的10 Hz rTMS治疗后，治疗有效者基线和1周时的额中线θ功率显著高于无效者，这与健康对照组结果相似，提示θ活动可能是海马-前额叶功能储备的标志物。后续研究中，Bailey等[25]使用基于相位同步的静息态脑电连通性进行分析，发现静息态θ连通性对疗效具有预测意义，且连通性越高，疗效越佳。Woźniak-Kwaśniewska等[15]对此也有相似的发现，rTMS治疗有效的抑郁障碍患者的顶区θ功率更大。

(二)诱发电位：运动诱发电位(motor evoked potential, MEP)的幅值变化可反映大脑的皮质可塑性改变，作为皮质可塑性的衡量标准，MEP幅值变化也可以预测rTMS治疗的效果。Hinchman等[26]发现，初级运动皮质TMS诱导的MEP变化可作为10 Hz rTMS治疗疗效的预测因子，然而这一发现在iTBS中并未得到重复。Li等[27]的研究进一步表明，长时程增强(long-term potentiation, LTP)样皮质可塑性的变化与认知功能密切相关，LTP样皮质可塑性的恢复可能预示着认知功能的改善。具体而言，rTMS治疗后MEP幅值的增加与抑郁障碍患者的认知功能改善相关。Lee等[28]的听觉诱发电位(loudness dependence of auditory evoked potentials, LDAEP)研究显示，LDAEP响度依赖性高的患者较依赖性低的患者在临床评分方面有更大的改善。全局平均场振幅分析(global mean field amplitude, GMFA)可通过计算所有电极的脑电活动振幅的平均值量化大脑的整体反应，主要成分包括N45、N100和GMFA-AUC，能够反映TMS脉冲后不同时间范围的峰值振幅，适用于TMS-EEG研究中的脑电活动。Strafella等[29]的TMS-EEG研究表明，iTBS治疗后N100振幅下降，但N45振幅无变化，且有效者的N45振幅高于无效者；基线N100振幅越高，iTBS后抑郁评分越低；GMFA-*AUC*值较高的患者对rTMS治疗反应更佳。

三、神经影像学标志物

MRI通过多模态技术，如功能磁共振成像(functional magnetic resonance imaging, fMRI)、结构磁共振成像(structural magnetic resonance imaging, sMRI)和扩散磁共振成像(diffusion magnetic resonance imaging, dMRI)，比较rTMS治疗前后大脑形态、结构及功能的变化。结构方面，抑郁障碍患者的海马体积减少、前额叶皮质萎缩、额叶和丘脑灰质减少[30-31]。功能方面，抑郁障碍患者多个脑区(如杏仁核、伏隔核、纹状体等)和脑网络间存在显著的功能连接改变[32-34]。默认模式网络(default mode network, DMN)、中央执行网络(central executive network, CEN)和突显网络(salience network, SN)被认为是参与抑郁障碍病理生理机制的重要网络，这些网络间的连接异常与异常的激活模式被认为是抑郁障碍的关键脑网络机制。

(一)fMRI

1. DMN：DMN涉及认知和情绪调节，核心节点包括后扣带皮层、前扣带皮层(anterior cingulate cortex, ACC)、楔前叶、内侧前额叶皮层、顶下小叶和双侧颞叶皮质，在静息或睡眠时活跃，或许与反刍思维及负性情绪加工密切相关[35]。Ge等[36]于2017年发现rTMS治疗无明显改善的抑郁障碍患者治疗前DMN的网络内连通性及网络间连通性较高，这种高连通性可能反映网络僵化，限制rTMS诱导的神经可塑性，提示DMN分离程度可作为个体化治疗的筛选指标。Phillip等[37]发现，抑郁障碍患者rTMS治疗后的症状减轻与治疗前额叶前扣带回膝下部分(subgenual anterior cingulate cortex, sgACC)与DMN负功能连接强度呈正相关。sgACC作为边缘系统-皮层通路的关键节点，其与DMN的负向耦合可能反映情绪抑制通路的代偿潜力，负性功能连接越强，rTMS对DMN过度活跃的调控效果越显著。Batail等[38]的加速iTBS治疗(斯坦福疗法)研究显示，治疗后杏仁核与DMN之间的功能连接显著增强，且功能连接变化越显著，临床疗效越好。杏仁核作为情绪加工核心脑区，其与DMN连接的强化可能促进负性情绪信息的适应性整合，从而缓解症状。

2. SN：SN负责调节DMN和CEN之间的切换，并与边缘系统协作处理疼痛、情绪、奖励和动机，其主要功能区包括ACC、前脑岛、杏仁核、下丘脑和腹侧纹状体。Iwabuchi等[39]的研究发现，DLPFC-SN(即额岛网络)功能连接能够预测rTMS治疗的短期疗效，rTMS治疗无效者的SN连通性更高。Fan等[40]

也观察到，基线时SN分离程度越高，即SN与其他网络的连接越少，预示着rTMS治疗后抑郁症状的更多改善。SN的基线分离越正常，预示着抑郁障碍患者对rTMS的治疗反应越好。Phillip等[37]研究还发现，抑郁障碍患者治疗后海马–SN的连通性降低也预示着更好的疗效。Batail等[38]在斯坦福疗法的研究中还发现杏仁核SN之间的功能连接显著下降，且与临床疗效相关。Ge等[36]则指出，rTMS治疗无明显改善的抑郁障碍患者，其左岛–SN的连通性较高。

3. ACC：ACC作为一个多功能的脑区，参与多个脑网络的调节和功能，包括额叶–边缘网络、DMN、SN、前额叶网络和记忆网络等，通过其吻侧前扣带皮层(rostral anterior cingulate cortex，rACC) 与sgACC的差异化功能参与情绪–认知整合。Ge等[41]进一步研究发现抑郁障碍患者rTMS治疗后临床改善与sgACC和rACC的功能连接变化有关，基线时sgACC–右DLPFC的功能连接降低和rACC–左顶下小叶的功能连接升高预示着更大的疗效；sgACC-DLPFC的短期和长期分类准确率分别为84%和88%；rACC–顶下小叶短期和长期分类准确率分别为76%和81%；sgACC–右DLPFC功能连接降低可能反映情绪抑制通路激活，而rACC-IPL功能连接升高可能增强自我参照信息与空间注意的整合。Beaken等[42]的研究发现，加速iTBS治疗有效的患者的sgACC和内侧眶额皮质之间有更强的功能连接，内侧眶额皮质参与奖赏评估与决策，其与sgACC连接的强化可能促进正性情绪体验，抵消抑郁相关的奖赏系统功能减退。

4.其他脑区及网络：rTMS还可通过调节奖赏环路、边缘网络及感觉皮层的功能连接实现多靶点干预。Du等[43]发现左DLPFC–左伏隔核之间增加的负功能连接强度预示着治疗的有效性，且DLPFC–伏隔核之间功能连接强度与抑郁、焦虑症状的改善呈负相关。Avissar等[44]研究发现，左DLPFC与纹状体之间较高的功能连接预示着较好的治疗反应，DLPFC对奖赏环路的调控可能恢复动机–奖赏匹配，减少快感缺失。Long等[45]研究发现，rTMS可诱导健康对照左DLPFC与边缘网络的功能连接呈负相关增加，且这种负相关性在抑郁障碍患者中越高则rTMS治疗效果越好；边缘网络(包括海马、杏仁核及下丘脑)过度活跃是抑郁的典型特征，负性功能连接增强可能反映DLPFC对边缘情绪的抑制性控制提升。Zhang等[46]研究发现，视觉皮层的功能连接降低与抑郁症状改善有关，抑郁障碍患者静息态与任务态下视觉皮层的功能连接异常增高，但rTMS治疗后这种异常的功能连接正常化，视觉皮层功能连接异常可能干扰感知–情绪整合，其恢复提示rTMS对感觉–边缘通路的广泛调节作用。

(二)sMRI和dMRI：sMRI通过揭示大脑皮质厚度和白质微结构的变化，为理解治疗反应提供了生物学基础。Nestor等[47]通过结构协方差网络分析发现，在重型抑郁障碍患者中，左侧DLPFC的皮质厚度与iTBS和10 Hz rTMS治疗的疗效呈正相关，而sgACC皮质厚度与疗效呈负相关，表明特定大脑区域的结构特征可能预测治疗反应。Bose等[48]的纵向研究进一步证实了这一观点，其发现rACC较薄的患者对rTMS治疗的反应更好，且治疗后rACC皮层厚度的变化与疗效相关，这强调了基线皮质厚度在预测疗效中的潜在价值。Ge等[49]于2019年通过分析CEN、DMN和SN的结构网络完整性，发现CEN的完整性是rTMS疗效的一个强有力的预测指标，治疗无效者的CEN结构完整性较健康对照组更低，而有效者则与健康对照组无显著差异，揭示了网络层面的大脑结构变化与治疗反应的关系。Ning等[50]的dMRI研究指出，重型抑郁障碍患者内侧前额叶和外侧前额叶白质的微结构变化与rTMS疗效相关，特定的白质微结构指标组合可以预测HAMD评分的变化，这为rTMS疗效的预测提供了新的生物标志物。

四、生化相关标志物

相较于神经影像或电生理标志物，针对rTMS治疗抑郁障碍的生化标志物[如下丘脑–垂体–肾上腺(hypothalamic-pituitary-adrenal，HPA)轴及相关蛋白、炎性因子、神经营养因子等]研究仍处于初步阶段，但近年已出现部分探索性成果。

1.神经内分泌：HPA轴过度激活是抑郁障碍的核心病理机制之一。有研究发现，rTMS能够显著降低皮质醇水平，表明其可能对HPA轴具有调节作用且可改善抑郁症状[51]。Shi等[52]对53例重型抑郁障碍患者外周血环状DNA的研究发现，rTMS真刺激组患者的外周血*circFKBP8*表达较假刺激组显著升高，表明其可能参与rTMS诱导的神经修复过程。*circFKBP8*及其编码蛋白在抑制糖皮质激素受体核转位过程中发挥关键作用，通过这一机制减轻HPA轴的过度激活，从而可能介导rTMS的神经修复效应。Song等[53]的研究发现，抑郁障碍患者血浆中的circDYM水平降低，而在接受靶向视觉皮层的rTMS治疗后，circDYM表达上调，其变化与临床症状的缓解

相一致，提示circDYM可能通过调节HPA轴下游信号通路发挥作用。

2.免疫炎性因子：炎性反应在抑郁障碍中扮演重要角色。Yilmaz等[54]、Wang等[55]均发现IL-6和CRP基线水平升高与较差的rTMS反应相关，但IL-1β、TNF-α等因子的结果尚不一致[56]，可能与样本异质性或检测方法差异有关。

3.神经可塑性相关分子标志物：神经可塑性在抑郁障碍的发病机制及治疗过程中具有重要意义。Gonsalves等[57]使用质子磁共振波谱测量右背侧前扣带皮层中的谷氨酸，发现基线水平较低的谷氨酸、谷氨酰胺和总N-乙酰天门冬氨酸与治疗后抑郁症状的更大改善显著相关。具体而言，基线谷氨酸水平较低的患者治疗后的抑郁症状改善程度更大。此外，基线谷氨酸水平较低的患者更有可能成为rTMS治疗的应答者。该研究还显示，基线BDNF水平较低的患者在rTMS治疗后，抑郁症状的改善程度更大，提示基线BDNF水平可能作为预测rTMS治疗反应的生物标志物。

4.遗传与表观遗传调控：Valiuliene等[58]得研究发现，在难治性抑郁障碍患者中，miR-146a-5p的低表达与rTMS疗效较差相关，其机制可能涉及对TRAF6/NF-κB通路的去抑制，导致小胶质细胞过度激活；而miR-146a-5p的高表达与更积极的治疗结果有关，其机制可能涉及神经可塑性相关通路(如mTOR、BDNF/TrκB)的表观遗传调控。

五、总结与展望

抑郁障碍的rTMS疗效预测生物标志物的研究领域尚处于探索阶段，相关研究仍面临着挑战，存在样本量不足、患者个体异质性大、抗抑郁药影响不明确等纳入与排除标准不统一的问题。此外，rTMS治疗参数的多样性，如刺激频率、靶点选择、刺激强度、治疗剂量、疗程长度及定位方法等，也为疗效预测带来了额外的混杂因素。各不相同的研究方法与统计学分析也进一步影响了结果的可靠性和一致性。未来仍需进一步扩大样本量，对目前研究结果进行复制并扩展，增加结果的可靠性并评估相关指标的稳健性。随着脑结构和功能检测技术的发展与进步，使用多模态联合、人工智能机器学习等手段，利用大数据平台，开展多中心联合研究，将为rTMS疗效预测生物标志物的研究提供新的视角和方法。这些技术的发展将有助于提高疗效预测的准确性，实现个体化治疗，从而为抑郁障碍患者提供更精准的治疗方案。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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