·综 述·

经颅磁刺激治疗神经病理性疼痛作用机制研究

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摘要 神经病理性疼痛(NP)是由躯体感觉神经系统损伤或疾病所引发的一种顽固性慢性疼痛,其发病机制复杂,临床治愈率较低,严重影响患者身心健康。经颅磁刺激(TMS)作为一种成熟的无创神经调控技术可以生成透过颅骨的短暂磁脉冲,诱导皮质神经元电位变化,对神经系统功能乃至结构产生影响,不仅能缓解NP相关症状,还可改善NP相关情绪障碍。但其镇痛相关的神经生物学机制尚未形成统一共识。本研究基于TMS作用原理,从调节突触可塑性、神经网络功能重组(诱导皮质-皮质间功能连接、诱导皮质下脑区间功能连接)、传入神经纤维敏感性、神经递质水平和神经免疫等方面综述TMS缓解NP方面的神经生物学机制,以期为TMS治疗NP提供依据。但还存在突触可塑性研究不够深入、传入神经纤维敏感性研究未进一步细化、神经免疫研究较为局限等不足之处,下一步研究还需开展多中心、大样本研究,采用颅脑脑电图等新型技术探讨TMS调控神经网络的内在机制,推广成对脉冲TMS在NP相关临床研究中的应用,为TMS治疗NP提供更可靠循证依据。

关键词 神经病理性疼痛;经颅磁刺激;突触可塑性;神经网络;神经生物学机制

神经病理性疼痛(neuropathic pain,NP)是由躯体感觉神经系统损伤或疾病所引发的慢性疼痛之一,其患病率3.3%~8.2%,我国目前约有4 620万例NP患者[1]。根据其病因可分为外周性和中枢性NP,包含在100多种临床疾病中,如脊髓损伤(spinal cord injury,SCI)、脑卒中后疼痛(central post-stroke pain,CPSP)、糖尿病神经病理性疼痛(diabetic neuropathic pain,DNP)和带状疱疹后遗神经痛(postherpetic neuralgia,PHN)等[2]。患者常表现为持续或间断的自发性疼痛,并可伴诱发痛、焦虑、抑郁、睡眠障碍和认知障碍等问题,严重影响患者生活质量[3]。目前治疗手段以药物治疗为主,包括抗癫痫药物(如加巴喷丁和普瑞巴林)、三环类抗抑郁药物(如阿米替林)、阿片类药物(如吗啡、羟考酮)等。但是,这些药物治疗效果不一,且具有成瘾风险和不可规避的毒副作用,对于中枢性NP患者,在12个月内其疼痛明显改善率仅为9.6%[4]。此外,脉冲射频、神经毁损等非药物治疗具有侵入性、风险较大、适应群体受限等问题。随着科学技术水平的不断提高,神经调控术凭借其高效、安全、绿色等优势正在成为NP的一种有效治疗方法。经颅磁刺激(transcranial magnetic stimulation,TMS)作为一种成熟的无创神经调控技术可以精准作用于指定皮层,生成透过颅骨的短暂磁脉冲,诱导皮质神经元电位变化,对神经系统功能乃至结构产生影响[5]。目前重复性经颅磁刺激(repetitive transcranial magnetic stimulation,rTMS)是TMS最常用的治疗模式,按照其刺激频率分为高频(>1 Hz)和低频(≤1 Hz),其中高频刺激可提高刺激部位神经元兴奋性,而低频刺激则起抑制作用。有临床指南已将靶向疼痛对

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侧初级运动皮质(M1)的高频经颅磁刺激(high frequency repetitive transcranial magnetic stimulation, HF-rTMS)作为缓解NP的A级证据[6]。除传统rTMS外,一种频率与大脑海马体θ波类似、更接近神经生理状态的Theta脉冲刺激(theta burst stimulation, TBS)也显示出其独特疗效,包括间歇性TBS(intermittent TBS, iTBS)和连续性TBS(continuous TBS, cTBS)。既往研究表明,NP的潜在病理、生理学机制较为复杂,涉及受损和邻近区域内神经元异常放电,影响一系列细胞及相关分子信号传导(包括离子通道改变、免疫细胞激活、表观遗传调控等),表现为神经元兴奋性持久升高的神经敏化、适应不良可塑性改变、下行抑制系统功能失活等多个方面[3]。其中,以中枢神经系统为主的神经敏化和结构功能上的广泛重组往往被认为是NP的主要发病机制之一[7]。但上述治疗手段证据质量仍较弱,其疗效机制相关研究也较少。本研究从突触可塑性、神经网络功能重组、传入神经纤维敏感性、神经递质水平和神经免疫等方面综述TMS缓解NP方面的神经生物学机制,以期为TMS治疗NP提供依据。

1 TMS影响突触可塑性

脊髓后角兴奋性神经元Rac1-GEF Tiam1通过介导突触结构、功能的异常可塑性,参与NP由发病到转变、维持的全过程[8]。YIN等[9]发现了位于背内侧前额叶皮质到中脑导水管周围灰质(periaqueductal gray, PAG)腹外侧区的通路具有疼痛下行抑制效应,但在慢性疼痛初始阶段,该通路内γ-氨基丁酸能神经元活动增强,通过抑制投射性神经元传递兴奋性信号,降低该通路对刺激性疼痛信号、疼痛诱发负面情绪的调控能力。突触结构和功能的可塑性改变是慢性NP形成的重要病理机制之一,且往往涉及多个脑区(如PAG、前扣带回、杏仁核等)[10]。

一项针对耐药性NP人群的研究表明,作用于运动皮质的rTMS治疗(20 Hz,干预5 d)镇痛疗效可维持1个月,且疗效优于iTBS,这可能与突触间信号传递率增加、恢复突触功能方面可塑性有关[11]。一项系统评价研究指出,*N*-甲基-*D*-天冬氨酸受体是TMS诱导突触可塑性所必需的[12],电压门控钠通道、L型电压门控钙通道也共同参与TMS诱导的长时程突触增强样变化。这种兴奋性变化可能会优先出现在近端树突上,进而介导突触的持久性改变,产生累积镇痛效应[13]。已有相关研究将TMS视为神经回路中调节突触功能的工具,发现TMS会影响突触超微结构及突触后膜神经递质释放[14]。THOMSON等[15]利用iTBS直接刺激由人神经母细胞瘤细胞(SH-SY5Y)分化的成熟神经表型,24 h后发现其可塑性基因NTRK2和MAPK9的表达明显增强。LUO等[16]通过监测果蝇大脑内投射神经元微型兴奋性突触后电流,发现rTMS以频率和强度依赖性方式调节神经可塑性,并以时间依赖性方式调节钙通道活性,揭示了rTMS可诱导神经可塑性活性的潜在机制。但对TMS如何通过诱导突触结构和功能的可塑性变化介导镇痛的具体分子、通路机制仍不完全清楚。

脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)作为突触形成和功能发挥的关键因子,还在一定程度上参与纹状体多巴胺释放[17]。ZHAO等[18]研究发现,急性中枢性NP患者在接受靶向M1区10 Hz rTMS后的疼痛缓解效应与血清中BDNF水平升高有关。抑郁个体中BDNF水平下调还将伴随突触可塑性降低、神经元萎缩,恢复这种异常改变将有助于改善抑郁状态和脑功能[19]。在NP急性期时,HF-TMS可能通过上调BDNF基因的表达水平,间接改善突触连接的微环境,保护受损神经元,减轻疼痛超敏反应诱发的异常疼痛[20]。随着研究深入,科研人员发现BDNF在NP慢性期存在过表达现象,这导致γ-氨基丁酸能、5-羟色胺能神经元介导的下行抑制系统功能减弱,加速突触异常可塑性和疼痛超敏反应的进程[21]。鉴于BDNF在NP病程中的复杂作用,合理利用这一生物标志物评估TMS有效性是今后研究的一大挑战。综上,TMS具有调节突触可塑性、改善疼痛及痛性情绪的潜力。

2 TMS恢复异常神经网络功能重组

研究发现,增强受试者脑内M1与PAG间的静息态功能连接可诱导机体强大的镇痛效应;相反,如果初级感觉皮层(S1)、杏仁核、岛叶等区域存在较强静息态功能连接,则会削弱下行抑制系统,促进上行疼痛信号的传递效能,放大机体对疼痛的感知[22]。皮质和皮质下神经网络的异常功能连接在NP患者中普遍存在,是痛感觉和痛情绪产生、维持的重要原因。TMS可以通过恢复刺激靶点和远隔区域间功能连接的正常化,发挥其独特治疗作用。

2.1 TMS诱导皮质-皮质间功能连接

HODKINSON等[23]基于M1与疼痛上行通路的竞争动态因果建模发现,1 Hz rTMS通过改变健康人群M1与岛叶皮层、前扣带皮层和顶叶皮层间功能

连接,发挥自上而下的镇痛作用。其中,岛叶皮层可塑性变化仅次于M1,揭示了M1与处理痛觉信息皮层之间的特殊网络连接,这可能是其发挥镇痛疗效的原因之一。一项针对中枢性NP患者的观察性研究结果显示,常规治疗1年后疼痛改善率为9.6%[6]。KIM等[24]依靠脑内代谢结合脑区功能连接、CPSP病灶逆向证实了存在于双侧M1、S1和枕叶皮质之间的特殊网络连接,20 Hz rTMS干预该疼痛网络后,其疼痛改善率高达85.7%。但考虑到NP病因复杂性、个体差异的多样性,NP相关皮质神经回路还有待更细致地研究。背外侧前额叶(dorsolateral prefrontal cortex,DLPFC)是继M1后另一重要靶点。YE等[25]基于脑电图观察到健康受试者左侧DLPFC接受10 Hz rTMS治疗后,其疼痛阈值提高并伴随DLPFC和岛叶皮层间N120振幅同步化增强。这为DLPFC重塑皮质间功能连接、间接激活下行抑制系统提供了有力证据。刘冬等[26]在M1和DLPFC采用10 Hz rTMS干预SCI患者,发现其在降低脑区内θ频段振幅、缓解疼痛、改善抑郁和焦虑情绪等方面均较单一脑区更优,这为推广TMS的多脑区联合干预方案提供了可靠支持。有研究认为皮质-皮质间功能连接变化与皮质兴奋性有关。CHIANG等[27]研究表明,伴有NP的多发性神经病患者皮质兴奋性指标短间隔皮质内抑制降低、皮质内促进增强,与M1投射到疼痛相关脑区(包括双侧丘脑、左侧S1和右侧M1)功能连接增加、疼痛强度、病变的感觉表型有关。此外,中枢性NP、DNP临床研究发现,患者运动诱发电位振幅、皮质内抑制指标较健康人明显降低,TMS治疗后可缓解疼痛并在一定程度上恢复皮质兴奋性[28]。但目前有关NP后皮质兴奋性变化尚未达成统一认识,这可能与个体基线、疼痛处理模式、NP异质性病因有关。因此,未来还需要进一步分析皮质兴奋性在疼痛中的作用,特别是重视其可能作为TMS镇痛指标的价值。

2.2 TMS诱导皮质下脑区间功能连接

M1作为缓解NP最常用的刺激靶点,其镇痛原理可能与重塑皮质下异常神经功能连接有关。有研究揭示了起源于M1层的特异性疼痛缓解环路:M1第5层神经元主要投射至PAG,可激活疼痛下行调制系统;而M1第6层神经元则主要投射至背侧丘脑和伏隔核的奖励环路,用于抑制疼痛引发的负面情绪和相关应对行为[29]。KADONO等[30]利用5 Hz rTMS干预CPSP灵长动物模型M1区,其对机械刺激和冷刺激的疼痛阈值明显增加、同侧丘脑背内侧核与杏仁核间功能连接恢复至基线水平,这可能与rTMS可恢复杏仁核对疼痛的调控力,有效减少上行疼痛通路对无痛性刺激的错误评估有关。未来有望将TMS精准靶向"层"为单位的脑结构,借此连接深层脑区功能。目前,越来越多的研究聚焦于疼痛下行抑制系统与高级皮层、皮质下区域之间结构和功能连接的改变。例如,PHN患者额叶皮层与PAG间的功能连接明显减弱[31]。动物实验研究显示,大脑皮层对下行疼痛抑制系统的驱动力丧失是疼痛超敏反应发生的基础,极大程度决定NP后续进展[32]。PAGANO等[33]推测作用于M1的rTMS可能会通过影响PAG、激活皮质-脑干投射通路、调节脑干内部下行调制系统,以缓解疼痛,但目前仍缺乏可靠基础研究证据。

3 TMS调节传入神经纤维敏感性

经典的"闸门控制学说"认为,脊髓背角神经元作为"闸门",受到细纤维(Aδ和C纤维)和粗纤维Aβ之间活性平衡的影响,调控痛觉信号的传递。目前,小纤维(Aδ和C纤维)病理学越来越被认为是NP的潜在因素,或许是导致伤害感受器致敏和变性的潜在机制之一[34]。在CPSP小鼠模型上,研究人员发现其C纤维敏感性较对照组明显降低,这可能与CPSP在机械刺激和热刺激下表现出的疼痛超敏反应有关[35]。涉及到传入纤维敏感性的深刻改变,即低阈值刺激也会导致疼痛产生,破坏感觉信息传递系统的正常运作。JONAS等[36]研究发现,不管是动物还是人类在接受4 Hz正弦电刺激后均会优先激活皮肤C纤维,但由于缺乏应对伤害性刺激的适应性调节,其轴突过度兴奋从而导致持续性疼痛加剧,表现为NRS疼痛量表评分增加。尽管这些研究由于样本量的限制,无法对不同病因来源的NP得出统一确切结论,但在一定程度上可为揭示NP的发病机制提供切入点。

此外,LENOIR等[37]研究显示,靶向岛叶皮层深部的cTBS可降低健康人双侧Aδ纤维对热痛的感知,但不影响其觉察正常的冷觉、热觉、触觉等,这提示深部cTBS可在保护皮肤感觉的基础上,选择性抑制异常疼痛产生。LI等[38]将延长性cTBS(由3个50 Hz脉冲组成、间隔200 ms、重复400次)与传统10 Hz rTMS、iTBS比较,结果显示作用于健康青年受试者左侧M1的单次延长性cTBS可明显提高双侧DLPFC和前额叶皮层兴奋性,增加Aβ纤维疼痛耐受阈值、提高TMS仪器使用效率,这提示延长性cT-

BS或许在一定程度上可以精准地调节传入神经纤维对于痛觉的感知，获得较持久的镇痛作用。延长性cTBS有望成为NP尤其是外周性神经病理性疼痛的替代疗法之一。

4 TMS影响神经递质水平

内源性阿片类物质（endogenous opioid，EOP）和多巴胺（dopamine，DA）主要负责调控疼痛相关负面情绪，并对NP患者行为产生持久影响。此外，体内阿片受体和DA水平还将影响种族、性别等个体因素对NP的易感性[39]。在NP发病初期阶段就可以检测到EOP和DA能信号传导分子在基因转录水平上的失调[40]。有研究从神经环路水平揭示疼痛信号可通过多个亚群特异性环路（如脊髓-臂旁-中脑环路、内侧被盖核-腹侧被盖区投射环路）抑制伏隔核中DA释放[41]。

有研究发现健康受试者在接受阿片类拮抗剂纳洛酮给药后，明显降低靶向右侧M1 10 Hz rTMS的镇痛效应，这提示HF-rTMS可激活富含μ阿片受体的内源性阿片系统[42]。LAMUSUO等[43]研究对健康受试者接受右脑S1/M1皮层的10 Hz rTMS治疗4 h，采用正电子发射断层扫描（positron emission computerized tomography，PET）发现左脑岛盖部和DLPFC上I-阿片受体示踪剂结合的改变，而非优势半球则集中在前扣带回、腹侧纹状体等。上述研究表明，TMS会通过激活不同类型阿片受体，诱导较为持久的内源性阿片物质释放。由于神经递质受体的空间分布差异，不同半球的同源脑区在疼痛处理过程中会表现出偏侧化性质。此外，TMS既可直接促进多巴胺释放，又可在受体水平上通过调节多巴胺信号传导、影响多巴胺D2受体（dopamine receptor D2，DRD2）依赖性细胞周期素依赖蛋白激酶5（cyclin-dependent kinase 5，CDK5）和突触后密度蛋白-95（postsynaptic density protein-95，PSD-95）蛋白水平、诱导突触可塑性变化，从而发挥镇痛作用[44]。一项有关健康受试者接受10 Hz rTMS治疗114 min后的研究，研究人员注意到同侧眨眼反射的习惯性增强，这是一种非侵入性间接测量中枢神经系统中DA活性的方式[43]，但并未通过PET观察到其多巴胺D2/D3受体拮抗剂与DA受体结合的变化。这项研究提示，尽管rTMS可能在一定程度上引发黑质纹状体多巴胺系统激活，但无法引起DA释放呈现持久可测量性的改变。TMS的效应发挥仍与DA息息相关。HONG等[45]研究发现，左侧DLPFC的10 Hz rTMS效应会受到多巴胺信号转导的遗传变异影响。OJALA等[46]使用10 Hz rTMS干预CPSP患者M1和次级感觉皮层（S2）的交叉试验发现，DRD2 rs6277基因型与M1镇痛效应明显相关，即DRD2 T/T型人群似乎比杂合子或C/C型人群更容易对TMS刺激产生反应。因此，携带高多巴胺转导的等位基因个体可能会对TMS治疗产生更多变化，这在一定程度上为不同人群选择高效镇痛治疗方案提供理论依据。

5-羟色胺（5-hydroxytryptamine，5-HT）作为脑干内疼痛下行调制系统中重要的单胺类神经递质，其功能失调、受体类型、分布密度将影响机体情感、行为等生理功能。一项针对犬类左前额叶皮层进行加速HF-rTMS干预研究，PET显示其亚属前扣带回皮层中血清素转运蛋白可用性降低，间接提高细胞外5-HT水平[47]。MURGAŠ等[48]研究发现，难治性抑郁症患者在接受作用于DLPFC区双侧序贯TBS治疗后，有效降低患者汉密尔顿抑郁量表评分，这可能与调控5-HT 1A受体的特异性分布体积有关。因此，TMS可能通过影响5-HT含量、受体分布密度，对疼痛相关负性情绪起积极改善作用。综上，体内神经递质水平不仅从多方面影响NP的发生发展，决定机体对疼痛的处理方式，还是TMS起效的重要靶点之一。

5 TMS调节神经免疫

在疼痛传导通路层面的神经免疫炎症被视为疼痛超敏反应的促进剂，其涵盖了几乎所有免疫细胞类型（包括炎症介质、细胞因子、趋化因子等）。TMS以神经免疫机制作为镇痛靶点，通过减少促炎因子[白细胞介素-1β（interleukin-1β，IL-1β）、白细胞介素-6（interleukin-6，IL-6）和肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）]，增加抗炎因子IL-10、神经营养因子、调节巨噬细胞、神经胶质细胞激活和极化平衡发挥其对NP的治疗作用[49]。

在坐骨神经慢性压迫性损伤（chronic constriction injury，CCI）的大鼠模型上，HU等[50]发现10 Hz rTMS通过mGluR5-NMDAR2B炎症信号通路，在降低皮质内代谢型谷氨酸受体5（metabotropic glutamate receptor 5，mGluR5）、NMDAR2B、TNF-α、IL-1β和IL-6等炎症介质水平方面明显优于1 Hz rTMS，有效缓解了CCI模型大鼠痛觉过敏和绝望行为。TOLEDO等[51]观察到5 Hz rTMS可能通过阻断脂多糖和IL-1β对突触长时程增强的损害，提高大鼠海

马体IL-10水平，改善异常性疼痛，逆转疼痛引发的长期认知障碍。这表明促炎因子和抗炎因子的平衡与TMS效应的发挥关系密切。此外，有研究发现，iTBS干预后的SCI大鼠皮质内巨噬细胞甘露糖受体（CD206）蛋白水平增加，而CD68和C-C趋化因子受体7（C-C chemokine receptor type 7，CCR7）蛋白水平降低[52]。这提示，iTBS通过上调M2型巨噬细胞高表达来调节巨噬细胞极化水平。一方面，抑制炎症反应，间接参与皮层神经元保护，改善皮质内微环境；另一方面，M2型巨噬细胞较M1型巨噬细胞可释放高达5.8倍内源性阿片类物质，可直接参与镇痛效应。除脑内神经免疫外，20 Hz rTMS还可抑制背根神经节中一氧化氮合酶（neuronal nitric oxide synthase，nNOS）过表达，逆转NO还原诱导的γ-氨基丁酸能去抑制。此外，iTBS还可诱导SCI大鼠生长相关蛋白-43（growth-associated protein-43，GAP-43）在脊髓和大脑中表达增加[53]。未来TMS有望作为安全的非药物治疗工具，一定程度上替代nNOS的抑制剂、延长N-甲基-D-天冬氨酸受体拮抗剂效应、参与修复神经损伤和缓解NP症状。

研究发现，神经胶质细胞对NP具有双重调控作用，可释放胶质源性神经营养因子、吞噬坏死细胞碎片，在神经保护方面起积极作用；但过表达的胶质细胞则介导神经炎症，参与痛觉超敏，推动NP慢性化进展[54]。一项系统评价研究肯定了HF-rTMS、iTBS、cTBS在疾病模型通过介导神经胶质细胞实现的神经保护价值，其中HF-rTMS不仅可以降低疼痛急性期内小胶质和星形胶质细胞反应性和衍生促炎因子；还可在一定程度上诱导少突胶质细胞增殖，促进髓鞘生成[55]。GAVA-JUNIOR等[56]研究显示，HF-rTMS通过调控星型胶质细胞释放多种胶质源性神经营养因子，激活神经元c-fos和ERK1/2蛋白表达，从内外2个部分修复损伤神经元，发挥特有神经保护功能。这种神经保护效应极度依赖于刺激频率，目前公认HF-TMS具有较高可重复性。KIM等[57]在SCI大鼠L_4、L_5平面上观察到25 Hz rTMS干预8周后，其小胶质细胞和星型胶质细胞特异性标志物离子钙结合衔接分子1（ionized calcium-binding adapter molecule 1，Iba1）和胶质纤维酸性蛋白（glial fibrillary acidic protein，GFAP）表达明显降低，提示HF-rTMS对过度活化胶质细胞的抑制作用与疼痛缓解有密切关系。此外，TMS还能通过调控多条信号通路[如核转录因子NF-κB（nuclear transcription factor-κB，NF-κB）、热隐蛋白2、Toll样受体1（Toll like receptor 1，TLR1）]，降低促炎型胶质细胞转录因子水平，调节胶质细胞间的表型平衡，改善神经炎症反应。因此，在神经炎症动态进展中，正确识别并利用胶质细胞的双重调节功能是更好发挥TMS效应的重要因素之一。

6 小结与展望

TMS能够通过调节突触可塑性、神经网络功能重组、传入神经纤维敏感性、神经递质水平、神经免疫发挥其独特镇痛效应。尽管TMS在镇痛领域已经展示出其独特优势，但还有很多不足之处。① 突触可塑性研究不够深入：目前实验局限于突触后膜神经递质释放率，缺乏TMS干预后细胞、分子层面有关突触超微结构或功能的研究。虽然皮质兴奋性变化可在一定程度上反映脑内神经可塑性，但由于个体差异等因素导致皮质兴奋性仍难以作为诊断、评估NP的可靠指标。② 传入神经纤维敏感性研究未进一步细化：针对传入神经纤维敏感性开展的试验仍非常有限，且尚未考虑受试者年龄跨度、性别等客观因素对神经敏感性的影响。③ 神经免疫研究较为局限：有关NP神经免疫的研究主要集中在动物模型上，难以向临床转化，TMS干预前后的关键炎症通路、细胞分子变化亦不明确。大多TMS镇痛靶点聚焦于M1区，对于其他潜在镇痛脑区（如DLPFC、脑岛部等）的有效性研究尚不充分。

下一步研究还需开展多中心、大样本研究；采用颅脑脑电图等新型技术探讨NP状态下脑区活动变化和TMS调控神经网络的内在机制，为选择高镇痛效率脑区与开展多脑区联合TMS治疗提供可靠支持；推广成对脉冲TMS在NP相关临床研究中的应用，实现TMS对NP的评估和治疗。综上，NP发生、发展与生物-心理-社会模式密切相关，多学科、个性化、多维度的综合康复疗法是未来发展的必然趋势，TMS或许会为NP临床治疗带来更多可能性。

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Mechanism of Transcranial Magnetic Stimulation Therapy for Neuropathic Pain

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ABSTRACT Neuropathic pain (NP) is a persistent and refractory chronic pain condition resulting from damage or disease of the somatosensory nervous system. Its complex pathogenesis, coupled with low clinical remission rate, significantly impairs the physical and mental well-being of the affected individuals. As a mature non-invasive neuromodulation technique, transcranial magnetic stimulation (TMS) can generate transient magnetic pulses penetrating through the skull, induce changes in cortical neuronal potentials, and affect the function and structure of the nervous system, which can not only alleviate NP-related symptoms, but also improve NP-related emotional disorders. However, there is no consensus on the neurobiological mechanism of TMS-induced analgesia. This study reviews the neurobiological mechanisms of TMS in alleviating NP from the aspects of regulation of synaptic plasticity, functional reorganization of neural network (inducing cortical-cortical functional connectivity and subcortical brain region functional connectivity), sensitivity of afferent nerve fibers, neurotransmitter levels and neuroimmunity based on the mechanism of TMS, in order to provide a basis for the treatment of NP by TMS. However, there are still some shortcomings, such as insufficient in-depth study of synaptic plasticity, the lack of further refinement in the research of the sensitivity of afferent nerve fibers, and the limitation of neuroimmune research. It is necessary to carry out multi-center and large sample studies, explore the mechanism of TMS regulating neural network by using new techniques such as cranial electroencephalogram, and promote the application of paired-pulse TMS in clinical research related to NP, so as to provide more reliable evidence for the treatment of NP with TMS.
KEY WORDS neuropathic pain; transcranial magnetic stimulation; synaptic plasticity; neural network; neurobiological mechanism
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Item Response Theory Model for Functional Assessment of Spinal Muscular Atrophy Based on the Hammersmith Functional Motor Scale Expanded

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ABSTRACT **Objective** To establish an item response theory (IRT) model for functional assessment of spinal muscular atrophy based on the Hammersmith functional motor scale expanded (HFMSE). **Methods** A total of 23 patients with SMA treated with corrective treatment in the Department of Geriatric Neurology and Pediatrics of the First Affiliated Hospital of Nanjing Medical University from February 2021 to June 2023 were included. Stack design was used to construct item response models (IRMs) for repeated measurement data. The likelihood ratio was used to calculate the parameters of the discrimination degree, guessing degree, difficulty and patient ability level (θ) of the HFMSE items for the optimal model. Differential test functioning (DTF) was used to analyze whether the scale was biased by rehabilitation treatment or gender. Monte Carlo simulation was used to prove that the difficulty distribution of the model items was not affected by the sampling process, a person-item plot was drawn according to the median expected difficulty, and the differences of the difficulty of each item in the HFMSE scale and the patient ability levels between the first assessment and the follow-up assessment were also discussed. **Results** A total of 32 items were included in this study to construct four alternative models, of which the 3 parameter logistic model (3PLM) had the best goodness of fit (P>0.05, M_2 statistic=479.75). The caution degree of all items was 1 in 3PLM, and the discrimination degree, guessing degree and difficulty of the items were calculated. The model had no significant evaluation bias on the factors of gender and rehabilitation treatment. The results showed high reliability (Cronbach's α=0.955, LCRC=0.981) and validity [θ value was positively correlated with the original total score (r=0.99, P< 0.001)] of 3PLM, allowing conversion of the θ value of the patient's ability to total score of the scale by binomial transformation. A person-item plot showing the distribution of item parameters and individual parameters on the patient ability level (θ) scale was used to observe the relationship between θ values and item difficulties. **Conclusion** IRT model based on HFMSE can provide suggestions on functional assessment and decision-making in rehabilitation treatment for patients with SMA in different scenarios, but attention should be paid to its item guessing degree.
KEY WORDS spinal muscular atrophy; Hammersmith functional motor scale expanded; item response theory; functional analysis
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