康复学报
Rehabilitation Medicine

神经电刺激调控技术在脊髓损伤后康复治疗中的应用及效应机制

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收稿日期:2024-04-10;接受日期:2024-09-20
基金项目:国家自然科学基金青年项目(81704163);首都卫生发展科研专项自主创新项目(2024-2-4086);
河南省医学科技攻关计划联合共建项目(LHGJ20220609)
DOI:10.3724/SP.J.1329.2024.06015
开放科学(资源服务)标识码(OSID):

摘要 脊髓损伤(SCI)是一种严重的神经系统疾病,常导致患者运动、感觉和自主神经功能的严重障碍。神经调控电刺激技术在SCI康复治疗中展现出了广阔的应用前景。本研究就神经电刺激调控技术在SCI后康复治疗中的应用及可能的作用机制进行综述。文章主要介绍脊髓电刺激(SCS)、深部脑刺激(DBS)等侵入性技术和周围神经电刺激(PNS)、经颅直流电刺激(tDCS)等非侵入性技术在SCI后康复治疗中的应用。神经电刺激调控技术治疗SCI的作用机制可能与调节突触可塑性、促进神经再生与修复,调节神经网络兴奋性、促进神经环路重建,调节神经递质系统、改善级联炎症反应有关。神经电刺激调控技术可在一定程度上改善SCI后运动、自主神经功能,但目前仍无法快速针对各种SCI类型提供最适合的个性化治疗方案;针对不同节段SCI的具体刺激频率、强度、持续时间和波形等参数尚未形成统一共识。下一步研究应持续分析不同干预手段对不同节段脊髓损伤后神经功能障碍的疗效与具体机制,采取多模态、个体化调控方案;探讨电信号对于恢复SCI后运动、感觉功能的关键原理,根据脊髓的节段损伤类型、年龄和性别等制订神经电刺激调控技术应用的专家共识,以期为神经电刺激调控技术在SCI患者康复治疗的应用提供参考依据。
关键词 脊髓损伤;神经调控技术;电刺激疗法;轴突再生修复;康复治疗;效应机制

脊髓损伤(spinal cord injury,SCI)是中枢神经系统常见的严重损伤之一,常导致损害相应节段出现感觉、运动和自主神经功能障碍,根据致伤原因,可分为创伤性SCI和非创伤性SCI。创伤性SCI多由于外伤(交通事故、坠落、跌倒等)所致,非创伤性SCI多由于炎症感染、脊髓肿瘤、脊柱退行性病变和血管原因等导致[1-3]。SCI分为原发和继发2个阶段,在原发性损伤后由于血脊髓屏障破坏、神经元胶质细胞死亡以及炎症细胞渗透等启动复杂的继发性损伤级联反应,进一步扩大神经组织损伤区域,加剧神经功能障碍,对患者造成极大的生理、心理和经济负担。随着人口老龄化以及社会现代化不断提高,SCI发病率呈现逐年上升趋势[4-6]。

传统的治疗方法(如药物疗法、手术疗法等)虽然能在一定程度上缓解症状,但是往往难以完全恢复受损神经功能,无法有效治疗这种破坏性中枢神经系统疾病。有研究表明,利用电信号的神经调控技术是调节神经系统的治疗方法,其中脊髓电刺激(spinal cord stimulation,SCS)、深部脑刺激(deep brain stimulation,DBS)等侵入性技术被应用于治疗

引用格式:刘文慧,孙文婷,胡耐翀,等. 神经电刺激调控技术在脊髓损伤后康复治疗中的应用及效应机制[J]. 康复学报,2024,34(6):633-640.
LIU W H,SUN W T,HU N C,et al. Application and mechanism of electrical neuromodulation techniques for rehabilitation of spinal cord injury [J]. Rehabil Med,2024,34(6):633-640.
DOI:10.3724/SP.J.1329.2024.06015

SCI且取得了一定进展。研究表明，SCS与DBS可改善SCI后运动、感觉功能障碍并缓解SCI后疼痛，与运动康复治疗相结合，是治疗SCI后运动障碍的有效方法[7-8]。周围神经电刺激（peripheral nerve electrical stimulation，PNS）、经颅直流电刺激（transcranial direct current stimulation，tDCS）等非侵入性技术因操作简便、安全性高也受到广泛关注[9-10]。tDCS可通过调节神经网络活性、增强突触可塑性和改善神经递质分泌均衡性等方式，促进SCI后神经修复和功能恢复。此外，tDCS在治疗SCI后抑郁、焦虑等情绪障碍方面具有一定疗效。PNS可以明显改善SCI患者上肢/下肢功能、肌肉力量、关节活动度、膀胱/肠道功能和自主神经控制能力。但各种刺激调控干预参数、靶点、治疗SCI的具体机制以及与其他康复治疗方法联用的效果目前尚无明确定论。本研究就神经电刺激调控技术在SCI后神经康复领域的应用及其效应机制进行综述，以期为优化SCI后康复治疗的神经电刺激方案提供参考。

1　SCI后康复治疗的神经调控电刺激术式与效应

1.1　SCI后康复治疗SCS技术及其效应

SCS技术是基于1965年MELZACK和WALL提出的“门控理论”形成的一种对进入脊髓背角的伤害性传入神经具有调节作用的调控技术，包括脊髓内、经皮和硬膜外刺激[11-12]。植入性的硬膜外脊髓电刺激（epidural spinal cord stimulation，ESCS）通过植入脊髓硬膜外间隙的电极产生微弱电流，在特定频率下刺激脊髓，改善由于外伤、退行性疾病等原因导致的神经功能障碍[13-14]；也可通过电刺激阻断疼痛信号通过脊髓向大脑传递，使信号无法到达大脑皮层，同时促进内源性镇痛物质的释放，进一步控制SCI后神经病理性疼痛（neuropathic pain，NP），目前已被广泛应用于神经系统康复领域（如SCI、NP、癫痫和脑卒中等）。由于外伤性SCI存在明显的物理压迫，此时进行SCS效果较好，能够减轻压迫，缓解症状。而对于缺血性SCI，由于血管闭塞导致的缺血、缺氧性损伤，SCS技术可能无法有效改善局部血液循环，其效果可能不佳甚至会加剧缺血状态，进一步损害脊髓功能。制订SCI治疗方案时，应充分考虑患者的个体差异和病情特点，如根据损伤脊髓的相应节段、运动或感觉功能障碍等制订个性化的治疗方案，寻找适合特定患者的最佳刺激参数。

SCS技术可恢复SCI患者行走功能，减轻SCI后疼痛，改善生活质量[15-16]。LORACH等[17]研究发现，脑-脊柱接口介导的硬膜外电刺激和肌肉刺激（epidural electrical and muscle stimulation，EEMS）的双电刺激神经康复方法可改善神经功能，从而恢复SCI后瘫痪患者对站立和行走的适应性控制。有实验研究表明，10～20 Hz EEMS双重刺激可在中枢模式发生器（central pattern generators，CPG）介导下模仿感觉反馈和前馈肌肉收缩回路，促进脊髓感觉运动回路结构和功能重建，恢复SCI大鼠感觉、运动神经环路的多突触电传导功能和后肢运动功能[9,18]。以上研究表明，SCS可以调节感觉信号传导，促进受损神经修复，从而改善SCI后神经运动、感觉功能障碍。EEMS可与其他康复治疗方法相结合，形成综合个体化治疗方案，更好地促进SCI患者康复。

1.2　SCI后康复治疗DBS技术及其效应

DBS技术是利用立体定向技术在特定的核团内精准放置刺激电极，随后释放高频电刺激，使相应核团兴奋或抑制，以改变脑内特定的神经电路活动。根据所选核团以及刺激参数不同，可产生不同治疗效果。目前DBS技术已被广泛应用于治疗帕金森病、肌张力障碍和特发性震颤等运动障碍，也可用于NP、癫痫治疗[19-21]。其神经调控作用、缓解疼痛和痉挛的潜力为SCI治疗提供了新思路，但具体疗效和安全性尚需进一步研究和验证。

神经康复训练是一个非常复杂的过程，涉及到多组肌肉不同程度的协调修复。DBS技术通过刺激特定脑区（如运动皮层、中脑、小脑等）可以影响脊髓神经传导和功能恢复。运动功能受CPG与脑干的运动中枢来源的信号所调节，其中关键的运动调节中枢是中脑运动区（mesencephalic locomotor region，MLR）［包括脑桥脚（pedunculopontine nucleus，PPN）和楔形核（cuneiform nucleus，CNF）］能够影响步态模式和节律[22-24]。临床随机对照研究表明，较低刺激频率（8～20 Hz）DBS可促进SCI后运动能力和神经功能康复[25-26]。HOFER等[24]和BACHMANN等[27]研究发现，MLR的DBS能够促进SCI后啮齿类动物运动功能与泌尿功能恢复，激活中枢神经系统自身调控通路，提高不完全性SCI的内源性修复。但是，SCI后脊髓损伤部位和范围各异，可能涉及多个神经核团和传导通路，如何准确选择刺激脑区靶点实现最佳疗效是一个关键问题。此外，DBS技术本身存在一定的风险和毒副作用（如感染、电极移位等）。在SCI患者中，这些风险和毒副作用可能更

为严重。虽然DBS技术对治疗SCI后运动功能、感觉功能障碍具有一定的潜力,但其是否应用于SCI患者康复治疗尚未形成统一定论。

1.3 SCI后康复治疗PNS技术及其效应

PNS技术是一种通过皮肤将特定的低频脉冲电流输入人体的非植入性电疗方法,也称为周围神经粗纤维电刺激疗法。该疗法主要通过刺激感觉纤维来发挥作用,通过兴奋A类纤维,关闭疼痛闸门和释放内源镇痛物质,从而缓解疼痛。PNS技术还可引起肌肉震颤收缩,改善局部血液循环,诱导相关肌肉皮质脊髓投射的兴奋性变化[28-30]。PNS技术具有非侵入性、安全性高、操作简便、长期疗效等优点,其在SCI康复治疗中受到关注,可用于改善SCI后运动功能、感觉功能和自主神经功能障碍。

在PNS过程中,非伤害感受的传入增加会造成T细胞突触前抑制,从而关闭脊髓到大脑皮质门阈,降低疼痛感觉[31]。肌肉和关节传入的感觉输入对皮层兴奋性的调节是感觉、运动整合的重要组成部分。多项研究表明,皮质脊髓束和周围运动神经配对关联刺激可通过突触前和突触后去极化诱导长时程增强(long-term potentiation,LTP)样效应,改善SCI患者运动功能[32-34]。BEEKHUIZEN等[35]也发现长时程PNS可激活特定运动区域,改善慢性不完全性颈椎SCI患者上肢功能、捏握力和神经可塑性,其具体效应机制有待进一步探析。因此,PNS技术可用于改善SCI后运动功能障碍、感觉障碍和慢性疼痛等症状。但未来还需进一步探索PNS的最佳治疗参数和疗效评估方法。

1.4 SCI康复治疗tDCS技术及其效应

tDCS技术是通过在头皮放置成对的阳极和阴极将微弱直流电施加于大脑特定区域,以调节皮层神经元的兴奋性,影响相关脑区功能的神经调控电刺激技术。tDCS技术通过调节神经网络的活性来发挥作用,改变神经元膜静息电位,从而调节神经元兴奋性[36-37]。与侵入性的DBS技术比较,tDCS具有非侵入性、操作简便、毒副作用小等优点,但存在刺激深度有限、空间定位不够精确等缺点。tDCS在中枢神经康复领域应用较为广泛。其中,tDCS可用于治疗SCI后运动功能、感觉功能、认知功能障碍和疼痛管理。

许多研究对tDCS刺激参数(如电流强度、刺激时间、电极位置等)进行优化,以期提高治疗效果。阳极tDCS通过锥体神经元细胞体去极化增加神经元兴奋性放电,阴极tDCS具有相反的超极化效果。其对皮质脊髓兴奋性的影响是通过膜受体上调或下调导致皮质突触的LTP或长时程抑制(long-term depression,LTD)样变化的结果,当刺激时间超过10 min可能会产生刺激周期以外持续数小时的效应存在[38-40]。TAN等[41]研究发现,tDCS对大脑运动皮层刺激可以作用于中脑和丘脑,缓解SCI大鼠模型神经性疼痛与运动功能障碍,抑制小胶质细胞向促炎的M1表型极化,促进其向M2抗炎表型极化,降低中脑和丘脑中肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)、白细胞介素-1β(interleukin-1β,IL-1β)等促炎细胞因子释放,改善SCI后的级联炎症反应。YOZBATIRAN等[42]研究发现,tDCS联合运动训练可改善SCI患者上肢功能和自主神经症状。

综上,SCS、DBS、PNS和tDCS技术均可以在一定程度上改善SCI后运动、自主神经功能,但这4种不同的神经电刺激调控技术刺激部位、优缺点各不相同。见表1。

表1 SCI神经电刺激调控技术常见类型

Table 1 Common types of neural electrical stimulation regulation technology of SCI

常见术式	刺激部位	优点	缺点
SCS	脊髓内、经皮和硬膜外	安全性高、微创、刺激参数可调节	患者筛选要求高、潜在并发症(如电极移位、感染)、治疗周期长
DBS	运动皮层、中脑、小脑等脑区	微创、可逆性和可调性	靶点选择困难、技术复杂、潜在并发症(如电极移位、感染)、长期疗效和安全性待验证
PNS	周围感觉神经	无创/微创性、安全性高、长期疗效	电极植入与定位较难、潜在并发症(如电极移位、感染)
tDCS	头皮等相应脑区	无创性、安全性高、改善多种功能	空间分辨率相对较低、刺激深度有限

2 神经调控电刺激术干预SCI的作用机制

神经调控电刺激技术作为一种常规神经康复手段。目前研究表明，其可能通过激活内源性神经修复机制、调节神经递质[谷氨酸、γ-氨基丁酸(gamma-aminobutyric acid，GABA)]释放、促进轴突再生和突触重塑等多种途径，改善SCI后的神经功能。此外，其还可能通过调节级联炎症反应、减轻氧化应激等机制，减轻SCI继发性损害，是SCI后运动、感觉等功能障碍的有效非药物干预措施。见图1。但是不同刺激参数产生的不同效应机制仍需进一步研究。

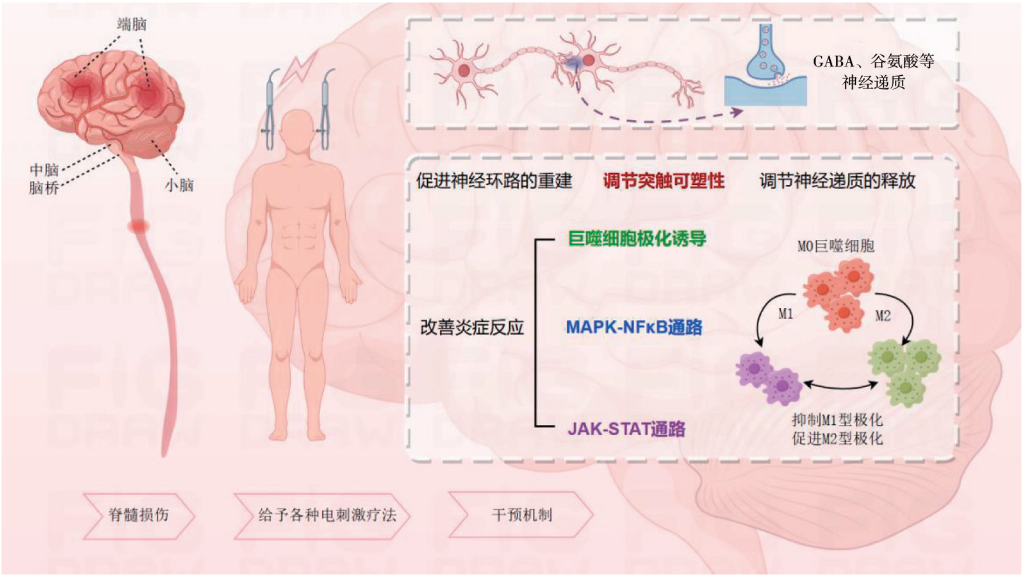

图1 神经电刺激调控技术干预SCI的作用机制

Figure 1 Mechanism of neural electrical stimulation regulation technology intervention in SCI

2.1 神经调控电刺激可调节突触可塑性，促进神经再生与修复

SCI后继发性外周运动轴突功能障碍会加剧肌肉萎缩，引起周围神经病变和神经性疼痛，甚至会进一步导致功能障碍。与低等脊椎动物具有明显再生能力的成熟中枢神经系统(central nervous system，CNS)神经元比较，人类CNS成熟神经元无法启动细胞内生长机制并再生切断的轴突，SCI后康复受制于此。电刺激信号可增加SCI后神经轴突再生标志物神经细胞胞浆蛋白9.5抗体(protein gene product 9.5，PGP 9.5)表达，增加抗凋亡相关性B淋巴细胞瘤-2基因(B-cell lymphoma-2，Bcl-2)蛋白水平，促进损伤脊髓电生理功能的恢复[43-44]。此外，PNS可通过反复的突触激活促进损伤部位神经元与升轴突和降轴突的动态整合和功能协调，增强谷氨酰胺能中间神经元和运动神经元之间神经突触可塑性，改善SCI后肢运动功能与自主神经功能紊乱[45-46]。

电刺激疗法还可激活内源性神经修复机制，在SCI后，内源性神经干细胞(neural stem cells，NSCs)可能会被激活并迁移到损伤部位参与神经修复过程。电刺激可进一步促进NSCs增殖和分化，促进神经生长因子表达，刺激神经细胞的增殖、迁移和分化，加速神经纤维再生和修复的进程[47-49]。

如何加速SCI后损伤神经再生与修复仍是较大的难题。NSCs具有自我更新和分化为神经元、星形胶质细胞和寡突胶质细胞的潜力，是SCI细胞治疗中最相关的候选细胞之一。通过移植外源性NSCs联合神经电刺激激活内源性NSCs等多种新兴综合管理治疗方案也许可以替代受损的脊髓细胞功能，促进神经再生和修复。但是，NSCs在宿主受损脊髓的中低长期存活和整合限制了治疗效果。未来研究应通过精确调控电刺激频率、强度、持续时间和波形等参数，最大化地激活内源性NSCs并促进其增殖和分化；深入研究电刺激对NSCs迁移、整合和神经纤维修复再生的具体作用机制；探讨加速SCI后康复过程神经再生与修复的综合个体化治疗方案。

2.2 神经调控电刺激可调节神经网络兴奋性，促进神经环路重建

脊髓中具有内在的神经回路，可以独立于大脑

产生活动,通常被称为CPG,其接受大脑下行运动命令产生节律性左右交替的躯体运动。SCI后损伤节段以下的神经纤维丧失髓上控制,会导致脑和脊髓运动神经环路连接中断,运动功能障碍或丧失[50-52]。经典解剖学研究发现,即使SCI损伤为完全性,大多SCI患者仍有一些残留白质纤维,腰骶髓神经元网络仍保留产生振荡、协调运动的输出功能。此外,临床试验与动物研究表明,SCS等电刺激疗法可以重新激活并利用损伤平面以下完整的运动和感觉纤维,重建神经环路,促进运动功能恢复[53-55]。PNS刺激大鼠尾部的感觉传入神经纤维可将电信号传递到腰骶段脊髓神经环路,激活CPG中间神经元、V2a神经元功能性沉默的兴奋性运动神经环路,促进大鼠瘫痪后肢的自主运动功能[46,56-57]。HARKEMA等[58]临床研究发现,使用不同电极组合、特定刺激参数和特定脊髓水平的EEMS,可以产生不同运动行为,使后肢瘫痪大鼠在有针对性的刺激后能够站立和行走。

尽管电刺激疗法在SCI后促进神经环路重建和运动功能恢复方面取得明显进展,但仍面临一些挑战:主要包括如何精确调控电刺激的参数以实现最大化治疗效果;如何根据受损节段优化电极设计和植入位置以提高刺激效率和长期维持治疗效果以促进神经环路的重建。因此,未来的研究应着手于神经科学、生物医学工程和康复医学等领域的跨学科合作研究以加速神经环路的重建过程。

2.3 神经调控电刺激可调节神经递质系统,改善级联炎症反应

原发性SCI后会产生一系列继发延迟性和进展性组织损伤,巨噬细胞、小胶质细胞等炎症细胞通过血脊髓脑屏障渗入损伤部位并向M1表型极化,通过MAPK-NFκB、JAK-STAT等通路触发TNF-α、IL-1β、IL-6等炎性细胞因子释放,产生级联炎症反应加重宿主细胞损伤[59-62]。此外,兴奋性和抑制性神经递质失衡也参与介导SCI后脊髓背角神经元的特征性变化。由于细胞释放谷氨酸等兴奋性氨基酸产生兴奋性毒性或通过抑制性GABA的减少进一步扩大神经元和胶质细胞的损失,促进SCI后NP的产生[63-66]。

电刺激治疗可抑制M1型炎症细胞的极化,降低炎症因子TNF-α、IL-6的表达,从而改善级联炎症和肌肉萎缩,促进SCI患者下肢功能恢复和生活质量提高[67-68]。研究表明,SCS可调节胆碱能、5-羟色胺能和阿片能系统相关性神经递质,通过激活M4毒蕈碱受体增加乙酰胆碱水平从而增强SCS介导的镇痛作用[69-70]。ROUSSEL等[71]研究发现,靶向CNF和PPN脑区的谷氨酸能神经元DBS可改善慢性SCI小鼠姿势和自发性运动功能恢复。

SCI后神经炎症失调会导致神经元和神经胶质细胞凋亡,形成抑制神经再生的萎缩性微环境。通过电刺激物理疗法抑制M1型炎症细胞的极化,降低炎性细胞因子释放,可以减轻脊髓炎症反应,降低神经毒性,保护神经元和组织免受二次损伤。未来研究可通过结合基因编辑技术、细胞治疗等策略,进一步优化电刺激疗法调节神经递质释放的效果。

3 小结与展望

多种神经调控电刺激技术已被广泛应用于SCI的干预治疗。运动功能、感觉功能及自主神经功能障碍是SCI后患者常见的症状,这将导致患者生存质量下降,加重疾病恶化与疾病负担。电信号干预的物理疗法作为一种新兴治疗方式,在SCI后康复中起到了重要作用。有创与无创的多项神经调控电刺激技术可通过激活内源性神经修复机制、调节神经递质释放和级联炎症反应等多种途径改善SCI后的运动功能,减轻并发的疼痛,为SCI患者提供了新的康复希望。但是,现有研究仍存在一定问题和挑战,无法快速针对各种SCI类型提供最适合的个性化治疗方案,针对不同节段SCI的具体刺激频率、强度、持续时间和波形等参数尚未形成统一共识。下一步研究应探讨不同干预手段对不同节段SCI后神经功能障碍的疗效与具体机制,采取多模态、个体化调控方案;探讨电信号对于恢复SCI后运动、感觉功能的关键原理,根据脊髓的节段损伤类型、年龄和性别等制订神经电刺激调控技术应用的专家共识。希望本研究可为神经电刺激干预SCI后康复提供参考依据,为患者带来更好的治疗效果和生活质量。

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Application and Mechanism of Electrical Neuromodulation Techniques for Rehabilitation of Spinal Cord Injury

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ABSTRACT Spinal cord injury (SCI) is a serious neurological disease, which often leads to severe impairments of motor, sensory and autonomic nervous functions. Electrical neuromodulation techniques have shown broad application prospects in the rehabilitation treatment of SCI. This study reviewed the applications and possible mechanisms of electrical neuromodulation techniques in the rehabilitation after SCI. It mainly introduced the applications of invasive techniques [spinal cord stimulation (SCS) and deep brain stimulation (DBS)] and non-invasive techniques [peripheral nerve stimulation (PNS) and transcranial direct current stimulation (tDCS)] in the rehabilitation after SCI. The mechanisms of electrical neuromodulation techniques in the treatment of SCI may be The mechanisms of electrical neuromodulation techniques in the treatment of SCI may be related to the regulation of synaptic plasticity to promote nerve regeneration and repair, the regulation of neurotransmitter system to improve the cascade of inflammatory response, and the regulation of neural network excitability to promote the reconstruction of neural circuits. Electrical neuromodulation techniques can improve motor and autonomic nervous functions after SCI to a certain extent, but they are still unable to quickly provide the most suitable personalized treatment plans for various types of SCI; there is no consensus on the specific parameters of stimulation frequency, intensity, duration and waveform for different levels of SCI. The future research should continue to analyze the efficacy and specific mechanisms of different interventions on neurological dysfunction after SCI at different levels, and adopt multimodal and individualized regulation programs; explore the key principles of electrical signals in the recovery of motor and sensory functions after SCI, and formulate an expert consensus on the application of electrical neuromodulation techniques according to the type of spinal cord segment injury, age and gender, so as to provide a reference for the application of electrical neuromodulation techniques in the rehabilitation of patients with SCI.

KEY WORDS spinal cord injury; neuromodulation techniques; electrical stimulation therapy; axonal regenerative repair; rehabilitation therapy; effect and mechanism
DOI:10.3724/SP.J.1329.2024.06015