



脑源性神经营养因子对周围神经损伤后 大脑皮层重塑的影响*

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摘要 周围神经损伤(peripheral nerve injury, PNI)不仅导致外周神经结构与功能障碍,还可引发感觉和运动皮层的显著重塑,表现为代表区沉默、侵占与功能性夺回,从而影响功能恢复预后。脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)作为中枢神经系统中关键的可塑性调节因子,在大脑皮层重塑中发挥重要作用。本文综述PNI后皮层重塑特征,包括感觉皮层代表区融合、运动皮层功能代偿及干预途径(如药物麻醉、跨模态激活等)。重点分析BDNF调控机制:通过促进树突/轴突生长、调控GABA能神经元成熟以维持兴奋/抑制平衡,以及通过介导N-甲基-D-天冬氨酸受体(N-methyl-D-aspartate receptor, NMDAR)依赖的长时程增强(long-term potentiation, LTP)突触可塑性参与皮层重组。同时,文章讨论了BDNF-TrkB信号通路、NMDAR依赖性调节以及遗传多态性(如BDNF Val66Met)影响重塑阈值,对皮层可塑性的影响。最后,结合当前研究进展,评估了基于BDNF的潜在临床干预策略及其在递送方式、安全性和个体化治疗方面面临的挑战,并提出“重夺阈值模型”指导干预时机。本文旨在为调控PNI后异常皮层重塑、改善功能恢复提供理论依据和新的研究思路。

关键词 周围神经损伤, 大脑皮层重塑, 脑源性神经营养因子, 神经可塑性, 长时程增强

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周围神经损伤(peripheral nerve injury, PNI)一般由外伤、疾病或手术等途径引起,是临床常见的创伤性疾病^[1]。周围神经系统(peripheral nervous system, PNS)相较于中枢神经系统(central nervous system, CNS)具有更强的再生能力,能够启动自主修复过程,但完全的功能恢复在临床上仍面临巨大挑战^[2]。PNI后的修复过程不仅依赖于周围神经自身的再生能力,其修复过程还涉及周围神经再生与中枢神经重塑的双重调控^[3]。

一方面,PNI会引发一系列局部反应,包括轴突和髓鞘的变性、施万细胞的活化、巨噬细胞的募集以及免疫微环境的调控,这些反应共同构建了一个有利于再生的微环境^[4-5]。在临床上,PNI后,对于损伤程度较轻、神经缺损较小的情况可以通过端对端缝合进行治疗^[6]。当神经缺损较大,无法通过直接端对端缝合修复时,通常需要采用神经移植进行桥接修复。目前,自体神经移植仍被认为是PNI修复的临床黄金标准^[7-8]。

但另一方面,即使神经修复,由于损伤部位的再生轴突发生错向生长,最后还会导致对肢体的再支配能力不能恢复到原来水平^[9]。临床和实验研究证明,PNI常导致运动协调和感觉定位的永久性障碍^[10],这是因为感觉运动皮层的传入信号丢失,感觉和运动皮层的代表区发生快速变化,即大脑皮层发生重塑,这种深刻广泛的功能重组,机体需要时间进行新的学习和适应^[11-12]。

传统观点认为,大脑发育“关键期”(critical period)结束后,可塑性显著下降,成年皮层被视为相对稳定的结构,但近年大量研究表明,与儿童期的强可塑及广泛的皮层重组相比,成年皮层仍保留着显著的损伤诱导性和经验依赖性可塑性^[13]。

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成年大脑的可塑性呈现“模块化”特征: 感觉皮层(如视觉、听觉等)的可塑性在青春期后明显减弱, 而运动皮层与前额叶皮层则在整个生命周期中持续保留较强可塑能力。这种区域差异提示不同脑区拥有相对独立的可塑性调控机制^[14]。

其中脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 在神经可塑性中扮演关键角色, 是神经系统功能的重要神经调节剂, 在神经元生长和存活, 神经传递和突触可塑性中起关键作用^[15]。本文以 PNI 后 BDNF 对大脑皮层重塑的影响进行讨论, 探讨 PNI 后调控大脑皮层重塑的新途径。

1 周围神经损伤后大脑皮层发生重塑

皮层结构和功能的完整性依赖于持续的外周信号输入与效应器官的正常反馈。当躯体局部感觉输入发生急性改变时, 例如病理条件下的感觉剥夺或额外的触觉刺激, 可引起大脑皮层功能代表区发生快速可塑性重组^[16]。PNI 后, 大脑皮层代表区 的重塑并非静态过程, 而是涉及有害侵占与有益复位的动态平衡。图 1 以正中神经损伤为例, 通过拼图形式直观展示了从正常分布→损伤沉寂与侵占→修复后代表区重新夺回的完整演变路径。

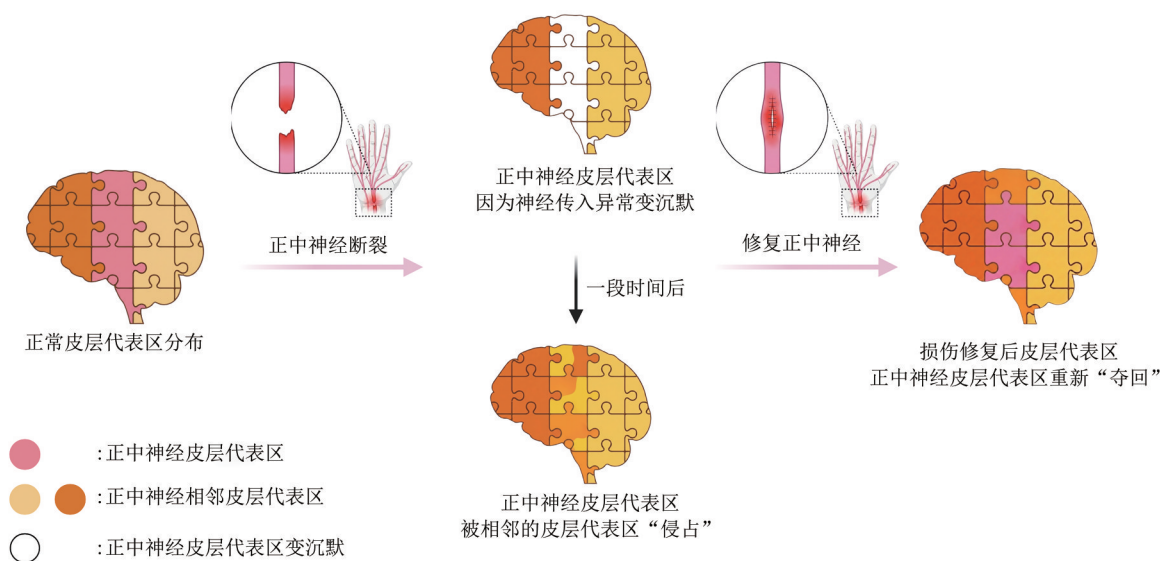


Fig. 1 Schematic diagram of cortical reorganization after median nerve injury
图 1 正中神经损伤后皮层重塑示意图

当正中神经损伤后, 正中神经皮层代表区立即发生沉寂。随着时间发展, 原有的皮层代表区被相邻皮层代表区“侵占”, 即有害重塑。如果采取手术修复受损神经后, 被修复的受损正中神经可“夺回”部分原正中神经对应的大脑皮层代表区, “夺回”的皮层区域越多, 患肢功能恢复就越好。而神经损伤后, 损伤神经对应的大脑皮层代表区被周围其他功能代表区“侵占”越多, 手术修复后, 被修复的受损臂丛神经对其原大脑皮层代表区的“夺回”就越困难。

1.1 感觉皮层发生重塑

身体某个部位的急性去感觉化或增加的触觉体验会导致大脑感觉皮层发生快速重塑^[17]。躯体感觉皮层发生重组最早证据来自灵长类动物, 研究人

员通过切断实验猴的正中神经, 对臂丛神经损伤后受损伤神经对应的皮肤进行刺激, 发现正中神经损伤对应的大脑皮层代表区明显丧失诱发活动, 接下来损伤的大脑皮层区域会对来自相邻皮层所对应的身体部位的刺激产生反应。随着时间推移, 皮层重塑逐渐稳定, 最终损伤部位的相邻皮层会占领去神经的皮层区域^[18-20]。同样, Rosén 等^[21]在临床上通过使用功能磁共振成像 (functional magnetic resonance imaging, fMRI) 发现, 长期暴露于手持振动工具导致手部感觉障碍的患者, 会表现出皮层重组的变化, 患者初级体觉皮质 (primary somatosensory cortex, S1) 中手指的皮层代表区融合, 激活的皮层体积显著增加。这种功能障碍源于患者长时间手持振动工具, 致使非生理性感觉长期

输入,并最终引发皮层重组^[21-22]。

1.2 运动皮层发生重塑

PNI后阻断了运动皮层输出信息向去神经支配肌肉的流动,从而导致瘫痪,初级运动皮层(primary motor cortex, M1)通过功能代偿和结构重组来适应外周神经功能缺失,这一过程涉及多层次的神经可塑性变化^[23]。

早期研究表明,面神经损伤后成年大鼠运动皮层内电刺激显示,原对应皮层代表区丧失肌肉诱发功能,而邻近前臂及眼睑的运动皮层代表区则出现于该区域,证实了PNI后运动皮层与躯体肌肉间突触连接的重塑^[24-25]。近期,利用7.0T fMRI技术的正中神经结扎(腕管综合征模型)研究进一步发现,损伤早期对侧初级感觉运动皮层、小脑及丘脑存在扩展性激活,提示中枢神经系统通过感觉运动皮层代表区的动态重塑,以代偿周围神经卡压引起的感觉输入缺失^[26]。

1.3 干预皮层重塑的多种途径及神经营养因子对PNI大脑皮层重塑的作用

目前已经有多种途径去干预PNI后大脑皮层重塑,干预旨在维持原有皮层代表区并促进皮层重组。如通过外界药物利丙双卡因(lidocaine and prilocaine)乳膏麻痹去感觉区邻近的皮层代表区扩张,维持去感觉区的原有皮层表征,改善手部感觉功能^[27]。或者躯体感觉皮层可以通过使用另一种感觉,例如听觉来代替缺失的感觉来激活。有研究表明,通过穿戴一个含有微型麦克风等传感器的特殊手套,不仅可以激活皮层的声觉区域,还可以激活听觉附近感觉区域,有效改善正中神经损伤修复后的触觉功能^[28]。还可以通过触觉想象练习和观察触觉的方式,通过对手的触觉刺激成像来激活体

感皮层。这种跨模态可塑性说明可以基于学习和经验动态调节皮层重组^[22]。

除此之外,在早期研究中,证明了神经营养因子,如BDNF、神经生长因子(nerve growth factor, NGF)、神经营养素(neurotrophin, NT)3和NT-4,调节电活动、突触传递和皮层内抑制^[29]。大脑可塑性的潜在机制也可能涉及电压门控系统,包括钠-钾-钙离子通道表达的变化^[30]。

在皮层的功能重组上,研究结果表明,神经营养因子在关键发育阶段对皮层重塑起着重要调节作用,它们可能参与成年哺乳动物在剥夺条件下的大脑皮层重塑^[31]。例如,Lodovichi等^[32]通过在大鼠关键期进行单眼剥夺并且在皮层内注射神经营养因子(如NGF、NT-4和BDNF)发现,高浓度的BDNF能够有效减弱单眼剥夺诱导的眼优势转移。

此外,BDNF还增加皮层突触的乙酰胆碱和谷氨酸释放,并调节视觉皮层的兴奋传递和突触效能^[32-33]。神经营养因子如BDNF、NGF、NT-3、NT-4在调控皮层重塑中起到积极作用,通过脑内注射,可以改善由于皮层重塑带来的负面影响,为PNI后的修复提供了思路。

PNI后,大脑皮层重塑是一个复杂的多分子参与过程。除BDNF外,NGF、胶质细胞源性神经营养因子(glial cell line-derived neurotrophic factor, GDNF)、NT-3与NT-4均被明确证实参与该重塑过程。它们共同调控神经元存活、轴突生长及突触可塑性等机制,从而协同促进中枢神经功能恢复^[34]。表1中比较了多种神经营养因子在PNI大脑皮层重塑中的作用及特异性,尽管多种因子在神经修复中存在协同效应,但其他因子的作用更多通过外周修复间接影响中枢重塑过程。

Table 1 Role and specificity comparison of multiple neurotrophic factors in PNI cortical reorganization

表1 多种神经营养因子在PNI大脑皮层重塑中的作用及特异性比较

神经营养因子	主要高亲和力受体	PNI中的主要生物学功能	对大脑皮层重塑的特异性作用机制	参考文献
BDNF	TrkB	维持中枢神经元存活,介导LTP	直接对中枢突触网络进行动态修饰,精准调控活动依赖性可塑性	[35]
NGF	TrkA	调控疼痛及周围神经再生	通过逆向运输,或上调脑内BDNF信号间接支持中枢修复	[36-37]
GDNF	RET/GFR α 1复合受体	促进运动神经元存活,改善神经炎症	受体机制非Trk家族,主要通过改善外周再生微环境间接影响中枢	[38]
NT-3	TrkC	神经元分化、轴突生长引导	损伤后在中枢星形胶质细胞中表达上调,辅助轴突再生	[39]

续表1

神经营养因子	主要高亲和力受体	PNI中的主要生物学功能	对大脑皮层重塑的特异性作用机制	参考文献
NT-4	TrkB	神经元存活、突触功能维持	与BDNF共享受体, 但在调控重塑方面作用较局限	[40]

BDNF: 脑源性神经营养因子 (brain-derived neurotrophic factor); NGF: 神经生长因子 (nerve growth factor, NGF); GDNF: 胶质细胞源性神经营养因子 (glial cell line-derived Neurotrophic Factor); NT-3: 神经营养索3 (neurotrophin-3); NT4: 神经营养索4 (neurotrophin-4); TrkB: 原肌球蛋白受体激酶 (tropomyosin receptor kinase); RET: 跨膜受体酪氨酸激酶 (rearranged during transfection); GFR α 1: GDNF 家族受体 α 1 (GDNF family receptor α 1); LTP: 长时程增强 (long-term potentiation)。

NGF 主要参与疼痛调控及周围神经再生, 通过逆向运输影响中枢重塑; 系统性阻断NGF可减轻神经损伤后的机械痛敏感性^[36]。糖尿病神经损伤模型中, NGF 治疗可上调前额叶皮层 BDNF 信号, 间接促进皮层修复^[37]。GDNF 主要显著促进运动神经元的存活和轴突的再生, 而外源性应用则可以改善神经导管修复效果^[38]。NT-3 通过 TrkC/ERK/c-Jun 通路维持去神经化施万细胞的修复表型, 促进慢性损伤后的周围神经再生, 其机制依赖 c-Jun 上调, 与 BDNF 通路存在差异^[39]。NT-4 与 BDNF 共享原肌球蛋白受体激酶 B (tropomyosin receptor kinase B, TrkB), 选择性促进施万细胞中髓鞘蛋白零 (myelin protein zero, MPZ) 表达, 参与髓鞘形成过程^[40]。

上述多种干预途径提示, 调控PNI后异常皮层重塑的关键在于深入理解其分子机制。BDNF 作为连接PNI信号与中枢可塑性变化的关键桥梁分子, 在成年皮层重塑的启动、扩展与稳定过程中发挥着核心调控作用。它不仅能响应去传入信号迅速上调表达, 还通过多层次机制 (结构可塑性、抑制性网络成熟及突触功能强化) 精细协调有害重塑与有益重塑的动态平衡。以下将重点阐述 BDNF 在 PNI 后大脑皮层重塑中的具体调控机制, 为后续针对性临床干预策略提供理论依据。

2 BDNF调控大脑皮层重塑

1982 年, 德国马普生物化学研究所的科学家从猪脑中分离出神经生长因子之后的第二个神经营养因子家族成员, 即 BDNF^[41]。BDNF 是调控神经元存活与突触可塑性的关键分泌因子^[42], 是哺乳动物大脑中分布最广泛、研究最广泛的神经营养因子之一, 尤其在海马体和皮层等区域高度表达^[43]。

图2中 BDNF 最初是以前体形式在内质网中合成并折叠为 BDNF 前前体蛋白 (pre-proBDNF)^[44], 前区序列通常在穿过高尔基体膜时被去除, 形成了脑源性神经营养因子前体蛋白 (precursor of brain-

derived neurotrophic factor, proBDNF), 随后 proBDNF 被细胞内外的蛋白酶进一步剪切, 最终形成成熟的 BDNF (mature BDNF, mBDNF)^[45-47]。

值得注意的是, proBDNF 与 mBDNF 具有相反的生物学效应: mBDNF 主要通过激活其高亲和力受体 TrkB 促进神经元存活、突触强化和神经可塑性^[48-49]; 而 proBDNF 则倾向于结合 p75 神经营养因子受体 (p75 neurotrophin receptor, p75NTR), 诱导突触修剪甚至细胞凋亡。这种双向调控机制使得 BDNF 在神经发育和功能维持中具有高度的时空特异性^[50-52]。

BDNF 不仅是一种关键的神经营养信号分子, 也是一种重要的神经调质, 对神经元的存活、分化、生长、修复以及突触可塑性具有核心作用^[53-54]。它不仅调控神经元和胶质细胞的发育进程, 还通过发挥神经保护作用及调节突触的短期与长期可塑性, 在认知功能和记忆形成中发挥作用^[55-56]。PNI 后, BDNF 在周围神经修复过程中发挥核心作用。损伤后, BDNF 在背根神经节 (dorsal root ganglion, DRG) 神经元、施万细胞、周围神经成纤维细胞及小胶质细胞中表达显著上调, 构成神经再生的关键分子机制^[57-59]。BDNF 通过激活 TrkB 受体及其下游 ERK/AKT 通路, 促进神经元存活、增强轴突内在生长能力、抑制远端神经萎缩, 并支持髓鞘再生与突触可塑性^[60-61]。

重要的是, BDNF 在 PNI 后大脑皮层发生重塑的过程中起到了关键作用, 目前 BDNF 主要通过以下 3 个方面影响皮层重塑。

2.1 BDNF促进树突、轴突生长

PNI 后, 去神经损伤部位的树突和轴突开始再生, 新生的轴突可能会被错误地定向到未受损的外周靶点, 导致皮层重塑^[62-63]。这种轴突错误的定向生长, 导致了外周输入和再神经支配的皮层代表区出现错误^[64]。Chand 等^[65] 研究指出, 大脑皮层树突的结构改变与损伤后的可塑性重组密切相关, 长期感觉剥夺可促使树突与轴突通过再生及侧枝发芽

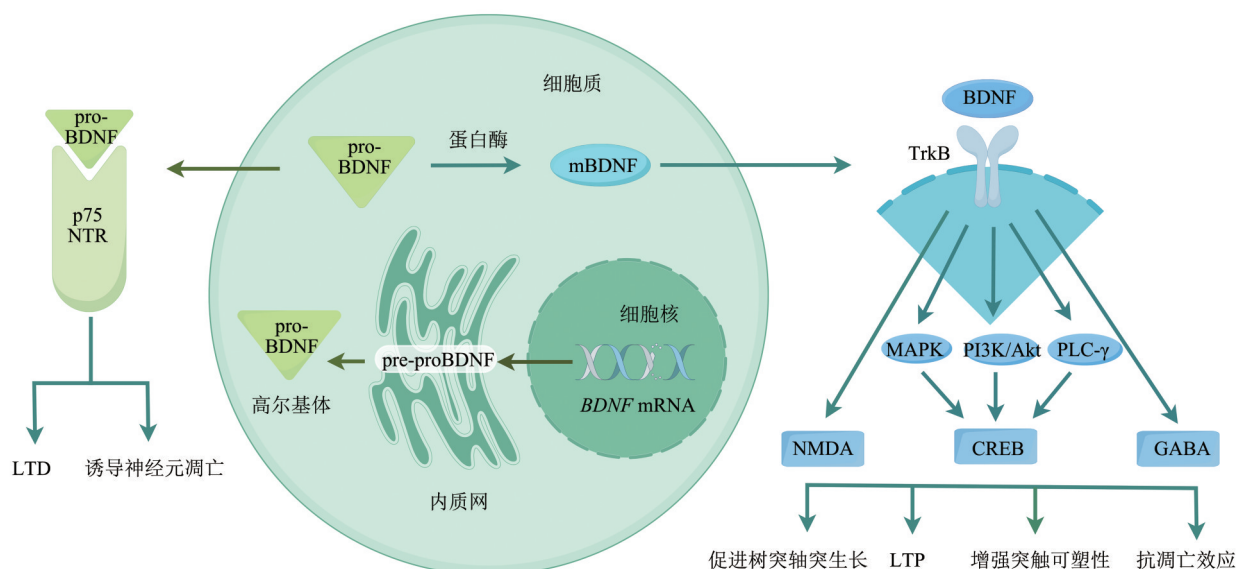


Fig. 2 Schematic diagram of BDNF signaling pathway

图2 BDNF信号通路示意图

BDNF的合成与加工过程。BDNF基因经转录生成mRNA，在粗面内质网的核糖体上翻译为前体蛋白pre-proBDNF；切除信号肽后形成约32 ku的proBDNF。proBDNF在高尔基体中被蛋白酶剪切为成熟的BDNF并分泌到胞外，也可被直接酶切转化为mBDNF。mBDNF主要通过激活其高亲和力受体TrkB促进神经元存活、突触可塑性和抗凋亡效应。proBDNF则倾向于结合p75神经生长因子受体，诱导LTD甚至细胞凋亡。mBDNF：成熟的脑源性神经生长因子（mature BDNF）；proBDNF：脑源性神经生长因子前体蛋白（precursor of brain-derived neurotrophic factor）；p75NTR：p75神经生长因子受体（p75 neurotrophin receptor）；LTD：长时程抑制（long-term depression）；LTP：长时程增强（long-term potentiation）；MAPK：丝裂原活化蛋白激酶（mitogen-activated protein kinase）；PI3K：磷脂酰肌醇3激酶（phosphatidylinositol-3 kinase）；PLC-γ：磷脂酶C-γ（phospholipase C-γ）；CREB：cAMP反应元件结合蛋白（cAMP response element-binding protein）；GABA：γ-氨基丁酸（gamma-aminobutyric acid）。

的方式实现再支配^[65-66]。

BDNF通过多种机制促进神经元树突和轴突的生长，进而调控大脑皮层重塑。其作用涵盖分子信号通路、局部蛋白质合成、细胞骨架调控等多个层面^[67-68]。研究显示，BDNF的自分泌与旁分泌均可促进皮层锥体神经元树突数量增加，但自分泌过表达所诱导的树突棘呈短暂性，使其稳定性降低，而旁分泌则无此效应，这可能缘于自分泌途径BDNF浓度更高^[69]。

Moya-Alvarado等^[67]在转基因小鼠皮层神经元中证实，轴突BDNF以cAMP反应元件结合蛋白（cAMP Response Element-Binding Protein, CREB）依赖方式促进胞体树突生长，该效应依赖轴突TrkB而非p75活性，表明轴突BDNF/TrkB信号具有促树突生长功能。此外，Ravindran等^[70]在大鼠皮层神经元中发现，BDNF通过诱导LIM结构域激酶1（LIM Domain Kinase 1, Limk1）的翻译调控，调节了树突生长，表明BDNF还可通过细致调节肌

动蛋白细胞骨架重组来介导树突发育。

在BDNF促进轴突生长方面，Charsar等^[71]在大鼠C2半切脊髓损伤模型中，采用脊髓内注射腺相关病毒2型（adeno-associated virus type 2, AAV2）表达BDNF，促进了膈肌运动神经元（phrenic motor neurons, PhMNs）区域的轴突生长。此外，BDNF还可促进特定微RNA前体向树突的运输，通过局部翻译调控树突发育，例如miR-132的活性依赖BDNF-TrkB信号^[72]。这些作用使BDNF在神经损伤修复和退行性疾病中展现出治疗潜力。

2.2 BDNF调控GABA能神经元

正常情况下，一些皮层区域功能可能被紧张性抑制所阻断。如果这些抑制被去除，相应区域的功能可能会很快增强，这一过程称为暴露。PNI后，大脑皮层出现快速重塑，受损神经对应皮层功能区被邻近皮层代表区迅速侵占，邻近皮层的这种扩张，可能是由于潜在的兴奋性突触连接暴露以及

γ 氨基丁酸 (gamma-aminobutyric acid, GABA) 抑制减少共同作用的结果^[73]。

利用磁共振波谱成像 (magnetic resonance spectroscopy, MRS) 分析发现, 人类感觉运动皮层中的 GABA 含量在去感觉化后几分钟内迅速降低^[74], 外周去感觉化导致丘脑和体感皮质中含有 GABA 或其合成酶——谷氨酸脱羧酶的神经元数量减少。服用 GABA 受体拮抗剂会增强对刺激的诱发反应, 并扩大躯体感觉皮层神经元的感受野^[75]。而 GABA 受体拮抗剂的使用, 又可以引起神经元突起延伸及诱发电位反应增强, 更加证实 GABA 在脑功能重塑中的作用。上述研究结果均表明, GABA 对保持皮层运动代表区具有关键性作用^[76]。

不同类型的神经营养因子可能作用于不同的神经元靶点, 并在这些靶点上调节神经元的电活动、突触传递的前后过程, 或者调控皮层内的抑制性连接^[77]。

研究发现, BDNF 在 GABA 能神经元正常成熟及依赖活动的可塑性中起关键作用, 加速 GABA 能神经元的形态和功能成熟, 通过促进抑制性神经元的成熟, 最终抑制了皮层重塑的持续可塑性, 而非直接增强重塑本身。其作用表现为对关键期时间窗的调控, 而非单纯促进或抑制突触变化^[78-80]。

关于具体信号通路, 最近有研究揭示, BDNF 通过激活 c-Jun 氨基端激酶 (c-Jun N-terminal kinase, JNK) 信号通路调控皮层 GABA 能中间神经元的成熟及神经元周围网络 (perineuronal nets, PNNs) 的形成。具体表现为: BDNF 通过 TrkB 受体激活 JNK, 促进谷氨酸脱羧酶 67 (glutamate decarboxylase 67, GAD67) 表达和 PNN 关键组分硫酸软骨素蛋白聚糖脑苷聚糖 (brevican core protein, Bcan) 和硫酸软骨素蛋白聚糖神经聚糖 (neurocan core protein, Ncan) 的合成, 加速中间神经元发育及关键期可塑性关闭, 这说明 BDNF 在神经重塑中的作用具有阶段性双重调控特性, BDNF 在生理条件下通过时空特异性调控, 既促进发育期功能性神经重塑, 又维持成熟期的稳定性, 而病理性的信号异常 (如持续 JNK 激活等) 可能打破这一平衡, 导致重塑能力受损^[81]。

除此之外, BDNF 还通过与其他系统交互间接影响 GABA 能神经元。例如, 在恐慌症模型中, BDNF 在背侧中央灰质 (dorsal periaqueductal gray, dPAG) 通过 TrkB 信号发挥抗惊恐作用, 该效应依

赖于 GABA-A 受体机制, 提示 BDNF-GABA 相互作用参与情绪调节^[82]。氯胺酮则通过增强 BDNF-TrkB 信号, 抑制麻醉诱导的 GABA-A 受体介导的异常电流, 从而改善术后认知缺陷^[83]。

2.3 BDNF 与长时程增强/抑制 (LTP/LTD) 介导的突触可塑性

在皮层重塑中, 中枢神经系统在较长时间内发生的可塑性重组可能涉及更稳定的功能或结构机制, 包括皮层内和皮层-皮层下的长时程增强 (long-term potentiation, LTP) 和长时程抑制 (long-term depression, LTD) 现象, 或通过轴突萌发和突触生成形成新的连接^[9, 84]。

有研究直接指出, 在失神经导致主导输入缺失后, M1 与 S1 中潜伏突触通过新激活模式被选择性加强并稳定。例如, 在大鼠模型中, M1 层锥体神经元的兴奋性突触传递先下降后回升至基线, 而抑制性传递先升高后持续降低, 伴随抑制性受体上调, 提示兴奋/抑制可塑性在修复中发挥相反作用 (兴奋性参与短期响应, 抑制性调控长短时程调节)^[85-86]。其至关重要的 LTP 和 LTD, 需要通过 N-甲基-D-天冬氨酸受体 (N-methyl-D-aspartate receptor, NMDAR) 的激活, 并依赖高浓度细胞内钙离子^[87]。

有实验表明, 灵长类动物正中神经断裂后, 如果在受伤后的第 1 个月内全身注射 NMDAR 拮抗剂, 手部皮层代表区的扩张就会减弱, 而在这一关键时期之后注射这种拮抗剂则不会产生这种效果^[88]。以上研究结果说明, NMDAR 在突触可塑性中起着关键作用^[89]。同时应注意 PNI 后 LTP 和 LTD 机制中特定神经递质的作用可能有时间依赖性。

BDNF 通过充当甘氨酸样配体调节 NMDAR 活性, 增加了 NMDA 通道的打开概率^[90], Leal 等^[91]发现, 用 BDNF 诱导培养的海马神经元会增加微小兴奋性突触后电流 (miniature excitatory postsynaptic current, mEPSC) 的振幅, 增强 NMDA 受体介导的钙离子内流, 诱导突触 LTP^[91-92]。

Huang 等^[93]通过在小鼠模型中基因敲除脑小胶质细胞的 BDNF, 并结合体内双光子成像技术, 发现小胶质细胞源性 BDNF 通过驱动 S1 的突触重塑和锥体神经元过度活动, 介导 PNI 后雄性小鼠的皮层可塑性和机械性痛觉过敏。另外 Hasan 等^[94]

研究表明, M1 NMDA 通过介导突触可塑性 (如 LTP) 和增强感觉-运动皮层 (sensorimotor cortex, S1-M1) 突触效能, 对小鼠联想学习至关重要。基因敲除 M1 皮层 *GluN1* 亚基导致 NMDAR 功能丧失, 显著损害眨眼条件反射和斯金纳箱任务的学习能力, 并阻断学习依赖的 S1-M1 突触强度增强, 证实 NMDAR 是皮层网络重组及行为学习的关键分

子基础。

BDNF 通过 TrkB 受体介导的多层次信号通路, 在 PNI 后皮层重塑的不同阶段发挥关键的时空特异性调控作用。该机制不仅桥接了外周损伤信号与中枢可塑性变化, 还决定了有害重塑与有益重塑的动态平衡, 为后续精准干预策略提供了分子基础 (图3)。

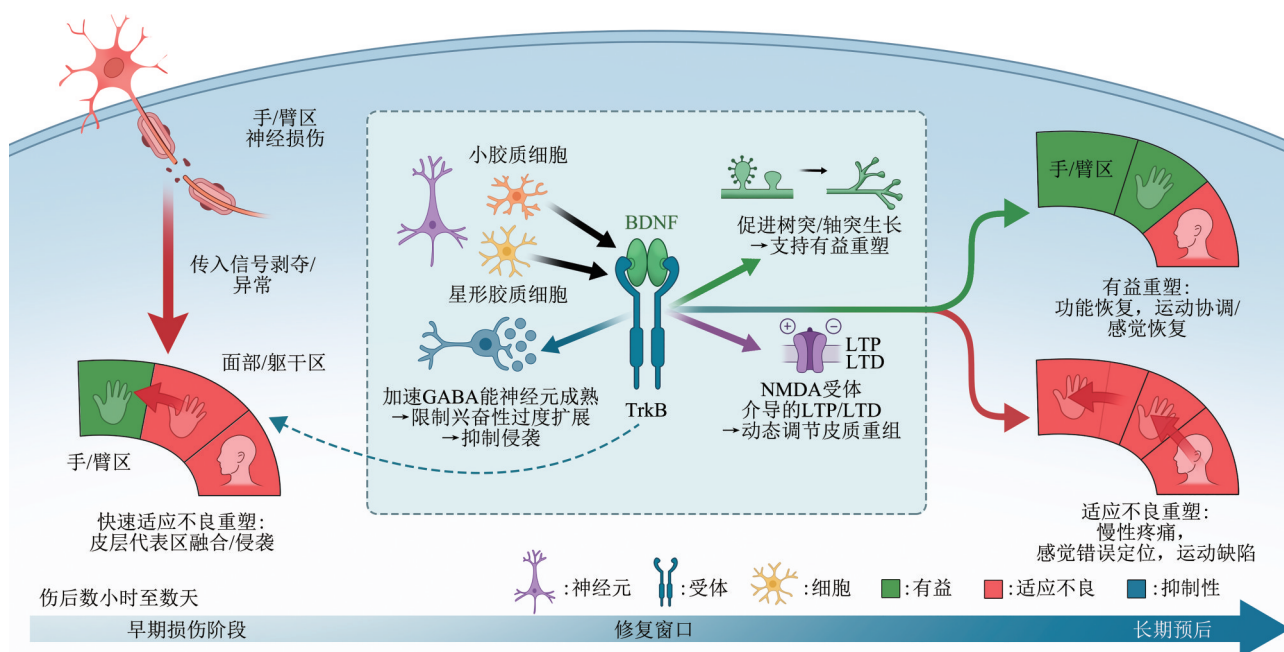


Fig. 3 Schematic diagram of the multi-level regulatory mechanism of BDNF in cortical reorganization after PNI

图3 BDNF在PNI后大脑皮层重塑中的多层次调控机制示意图

周围神经损伤 (PNI) 后, BDNF 表达上调并主要通过 TrkB 受体介导多层次调控网络, 促进大脑皮层重塑。BDNF: 脑源性神经营养因子 (brain-derived neurotrophic factor); TrkB: 原肌球蛋白受体激酶 B (tropomyosin receptor kinase B); LTP: 长时程增强 (long-term potentiation) LTD: 长时程抑制 (long-term depression); GABA: γ 氨基丁酸 (gamma-aminobutyric acid); NMDA: N-甲基-D-天冬氨酸 (N-methyl-D-aspartate)。

2.4 BDNF 三种调控机制的内在联系

上述树突/轴突生长、GABA 能神经元调控和 LTP/LTD 并非 3 个孤立的过程, 而是在分子通路、环路整合与功能输出层面存在深层协同, 共同构成皮层重塑的核心调控网络。

从图3中可以看出, 在分子通路层面上, TrkB 信号起到枢纽作用, BDNF-TrkB 轴突信号内体不仅能够将轴突末端接收到的信号逆向传递至胞体, 促进树突分支与突触结构重塑, 又增加 NMDAR 在树突棘的积累与稳定性, 直接将结构可塑性与 LTP 诱导耦合^[67, 95]。同时, proBDNF/mBDNF 的双向调控为这一网络提供了方向性: mBDNF 通过 TrkB

介导 LTP 和树突发育, 而 proBDNF 经 p75NTR 在杏仁核等区域特异性调控 LTD, 参与恐惧消退等学习过程^[96-98]。另外, BDNF 通过 JNK 信号通路促进 GABA 能中间神经元及 PNNs 的成熟^[81], PNNs 作为“可塑性刹车”, 其完整性直接影响 LTP/LTD 阈值与树突棘动态^[99-100]。而酶解 PNNs 可降低 JNK 活性、解除抑制, 重新开放幼年样可塑性, 这与成年皮质“受限但非僵化”的重塑机制高度吻合^[101]。

在哺乳动物大脑皮层神经环路中, 突触兴奋性 (excitation, E) 与抑制性 (inhibition, I) 之间的精确平衡 (excitation/inhibition balance, E/I

balance) 对于复杂行为的正常产生至关重要。BDNF/TrkB 信号通路不仅参与 GABA 能中间神经元的发育成熟, 还通过调节 I 和维持 E/I 平衡, 进而影响社会支配行为等高级社会行为^[102]。

BDNF 不仅通过 TrkB 受体激活 MAPK/ERK、PI3K/Akt 及 PLC γ 等信号通路, 促进神经元存活、轴突延伸、树突分支形成及树突棘成熟, 增强结构性突触可塑性^[103-104]。BDNF 同样是 GABA 能中间神经元成熟的重要调控因子。BDNF-TrkB 信号促进 PV 中间神经元发育及 PNNs 形成, 从而促进关键期关闭并增强皮层抑制性网络稳定性^[104]。成熟的 GABA 能抑制系统虽然会限制神经网络无限制生长, 但其作用并非单纯抑制可塑性, 而是维持兴奋/抑制平衡, 保证神经网络重塑的精确性和稳定性^[104]。

综上, BDNF 通过时空特异性的多层次调控机制, 在 PNI 后皮层重塑中扮演着关键的“双刃剑”角色: 适度激活可促进适应性重组与功能恢复, 失调则可能加剧有害重塑和慢性疼痛。这一机制洞见为临床转化奠定了坚实基础。如何将这些基础机制研究成果转化为安全有效的干预手段, 已成为当前亟待解决的核心问题。以下将重点讨论基于 BDNF 的临床转化策略、现有递送技术挑战, 以及结合前期皮层重塑机制的精准干预思路。

3 BDNF 临床转化策略与挑战

PNI 后大脑皮层重塑的分子机制研究, 特别是 BDNF 的多层次调控作用, 为开发针对中枢可塑性的治疗策略提供了重要方向。尽管基础研究已充分揭示 BDNF 在树突生长、GABA 能成熟及 LTP/LTD 中的关键作用, 但将其转化为临床应用仍面临诸多挑战, 包括高效递送、时空精准调控及个体化差异等。以下将结合 PNI 特异性临床前与临床证据, 系统评估 BDNF 干预策略的可行性与瓶颈。

目前研究已经证实, 囊泡关联膜蛋白 3 基因 (vesicle-associated membrane protein 3 gene, Vamp3)、TrkB 受体、TGF- β 1/SMAD3 通路及 NMDAR 是调控 BDNF 分泌的关键靶点, 抑制促炎因子肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α) 或增强抗炎信号沉默信息调节因子 1 (silence information regulator 1, sirtuin 1, SIRT1) 可间接促进 BDNF 释放^[105]。基于此, 基因递送 BDNF、靶向 EVs 分泌途径 (如 Vamp3 激活剂) 或

调节星形胶质细胞极化 (如 A1/A2 表型转换) 可能成为神经保护的新方向^[106]。

同时要注意, BDNF 本身药代动力学性质差 (如半衰期短、难以穿透血脑屏障), 需依赖载体系统 (如外泌体、病毒载体或纳米颗粒) 实现靶向递送^[107-108]。例如, 利用冷冻凝胶微载体实现 BDNF 缓释^[109], 通过纳米载体静脉给药改善阿尔茨海默病模型认知功能^[35]。

此外, 长期递送需平衡疗效与安全性, 避免高剂量 BDNF 激活 p75NTR 的神经毒性, 例如基因治疗中需避免过度表达导致的副作用^[110]。还需注意基于患者 BDNF 基因 Val66Met 单核苷酸多态性 (single nucleotide polymorphism, SNP) 制定分层方案^[111-112]。

对于 BDNF 的临床应用, 可以通过基因治疗发挥 BDNF 作用, 例如通过 AAV 载体递送 BDNF 基因至下丘脑, 可改善代谢综合征 (如 Prader-Willi 综合征) 的肥胖和胰岛素抵抗^[113]。AAV 介导的 BDNF 基因递送已在阿尔茨海默病、帕金森病临床试验中评估^[114]。有实验表明, 还可通过鼻内给药, 使用过表达 BDNF 的小型细胞外囊泡 (small extracellular vesicles, sEVs), BDNF-sEVs 能改善功能行为、减少脑梗死体积、增强神经再生和血管生成, 并降低炎症因子表达, 激活 BDNF/TrkB 信号通路, 发挥 BDNF 在脑损伤治疗中的潜力^[115]。研究证实, 负载 BDNF 的人脐带间充质干细胞来源外泌体 (BDNF-EXO), 经静脉注射后可穿透血脑屏障, 通过抑制神经元凋亡与铁死亡, 显著改善帕金森病模型的病理特征^[116]。

目前涉及 BDNF 干预 PNI 的临床实例研究非常有限, 绝大多数证据来自动物实验或体外模型。对于 BDNF 干预 PNI 的临床实例研究非常有限, 一项针对尺神经损伤患者的随机对照临床试验显示, 通过经皮神经刺激可以促进修复尺神经病变, 其中血液样本表明, 该干预可能促进了 pro-BDNF 转换为 mBDNF 促进神经再生^[117]。除此外, 目前涉及 BDNF 干预 PNI 的研究更多为临床前模型, 例如: 大鼠下牙槽神经损伤中外源性 BDNF 加速骨修复^[59]; 大鼠坐骨神经缺损模型中含缓释 BDNF 的复合神经导管促进再生^[118]; 小鼠坐骨神经损伤中通过基因修饰干细胞上调 BDNF 改善功能^[119]; 以及通过运动或药物激活 BDNF-TrkB 通路促进轴突再生等^[120-121]。

鉴于递送方式、安全性及个体化治疗仍是 BDNF 干预面临的主要瓶颈,表2对主流策略进行

了系统比较,以期为后续研究和临床应用提供参考。

Table 2 Comparison of BDNF-based delivery strategies

表2 基于BDNF的递送策略比较

策略类型	代表方法	优势	主要挑战	临床转化潜力	参考文献
基因治疗	AAV-BDNF	持久表达、靶向性强	免疫反应、剂量控制难	中等	[113-114]
外泌体/纳米载体	BDNF 包载的外泌体	血脑屏障穿透好、低免疫原性	装载效率、释放控制	高	[107-108]
蛋白直接递送	鼻内/植入泵	简单、安全	半衰期短、BBB限制	低-中等	[115]
复合干预	BDNF + 跨模态激活	协同增强可塑性	需多中心验证	中等	[120-121]

AAV-BDNF: 携带脑源性神经营养因子基因的腺相关病毒 (adeno-associated virus encoding brain-derived neurotrophic factor); BDNF: 脑源性神经营养因子 (brain-derived neurotrophic factor); BBB: 血脑屏障 (blood-brain barrier)。

综上,尽管 BDNF 在 PNI 修复中的潜力被大量动物实验支持,但临床转化研究仍十分匮乏,未来的临床转化需着力于开发安全可控的 BDNF 递送系统(如缓释导管、干细胞载体)^[122-123],目前外泌体和纳米载体在克服递送瓶颈方面最具潜力,结合跨模态激活有望实现精准干预。同时阐明 BDNF 时空表达的精确调控机制,避免疼痛等副作用,并推动多中心标准化临床试验,并整合基因治疗、物理治疗等联合方案,以实现从“促进再生”到“功能完全恢复”的跨越。

BDNF 临床转化需多学科协同突破递送瓶颈、深化机制认知并优化干预策略,当前纳米技术、基因编辑、非药物干预等方向已展现显著潜力,但仍需严谨验证以实现安全有效的临床应用。

4 结论与展望

PNI 不仅造成外周轴突与靶器官的结构功能损害,更通过剥夺或异常的感觉-运动传入,引发 S1 和 M1 代表区的快速重组、融合与功能代偿。这一中枢重塑过程既是功能恢复的生理基础,也是慢性疼痛、感觉错位和运动协调障碍的重要病理机制。

BDNF 作为连接外周损伤与中枢可塑性的关键分子桥梁,通过 TrkB 受体介导的多层次调控(树突/轴突生长促进、GABA 能抑制网络成熟加速、NMDAR 依赖的 LTP/LTD 动态调节),在皮层重塑的启动、扩展与稳定阶段发挥时空特异性的双向作用:适度、适时的 BDNF 信号支持适应性重组与功能复位,而信号失衡或持续异常激活则可能加剧有害重塑(如相邻代表区侵占)或促发病理性可塑性(如痛觉过敏)。

近年来,对提升 PNI 疗效的研究主要聚焦于两个关键环节:一是如何在神经损伤后,抑制受损神

经的原皮层代表区范围被邻近皮层代表区侵占,从而为后续神经修复后原代表区的功能性“复位”创造有利前提;二是如何在神经修复后,促进受损神经原皮层代表区的充分重建,以最大限度地恢复功能。

基于前期对臂丛损伤后皮层功能重塑的研究^[124-125],我们提出“皮层代表区重夺阈值模型”:损伤早期 BDNF-TrkB 通路的上调可通过增强 GABA 能抑制和限制兴奋性过度扩散,减缓邻近皮层对损伤代表区的“侵占”;而在神经修复后关键窗口期,适量 BDNF 递送则有助于促进修复轴突重新“夺回”原有皮层表征,实现有益重塑。该模型强调 BDNF 作用的强烈时序依赖性,并提示 BDNF Val66Met 多态性可能显著影响个体重塑阈值与干预应答,为 PNI 患者预后分层和精准干预提供了理论切入点。

值得注意的是,BDNF 介导的皮层重塑具有明显的双重效应:在适当的时间窗和剂量范围内,BDNF 信号可促进适应性皮层重组并支持感觉与运动功能恢复;而在信号失衡或持续异常激活的情况下,BDNF 亦可能参与异常皮层映射、感觉紊乱或慢性疼痛的形成。因此,如何精确调控 BDNF 信号的时序、空间分布及细胞来源,是实现神经功能重建的关键挑战。

展望未来,BDNF 相关研究与临床转化需在以下 3 个方向重点突破,以推动从机制解析向精准神经修复的跨越。

第一,利用单细胞/空间转录组学和光遗传学工具,系统绘制 PNI 后不同时间点、不同皮层亚区中 BDNF 来源加工形式(mBDNF、proBDNF)及其下游信号网络的动态图谱。特别需阐明 BDNF 与主要组织相容性复合体 I 类/配对免疫球蛋白样受体

B (major histocompatibility complex class I/paired immunoglobulin-like receptor B, MHCI/PirB)、炎症微环境之间的交互作用,以验证并优化“重夺阈值模型”。

第二,开发与验证BDNF安全高效递送系统,优先推进外泌体、纳米脂质体、冷冻凝胶微载体等非病毒递送平台,实现BDNF的血脑屏障穿透、皮层靶向缓释与可控释放。同时开展针对Val66Met基因型的剂量-效应分层研究,避免高剂量诱导p75NTR介导的毒性效应。

第三,通过设计多模态干预策略的临床前-临床桥接试验,整合BDNF靶向递送与跨模态激活(如听觉-触觉替代、镜像疗法、经颅磁刺激)的复合干预方案。建议在臂丛/正中神经损伤患者中开展多中心、前瞻性队列研究,联合fMRI、扩散张量成像和高密度脑电图(high-density electroencephalography, high-density EEG)动态监测皮层代表区变化与功能结局,建立BDNF生物标志物指导下的个体化干预决策路径。

通过上述方向的系统推进,有望将BDNF从“关键调控因子”转化为“可精准操控的治疗靶点”,最终实现从“结构修复”向“功能性神经重建”的范式转变。

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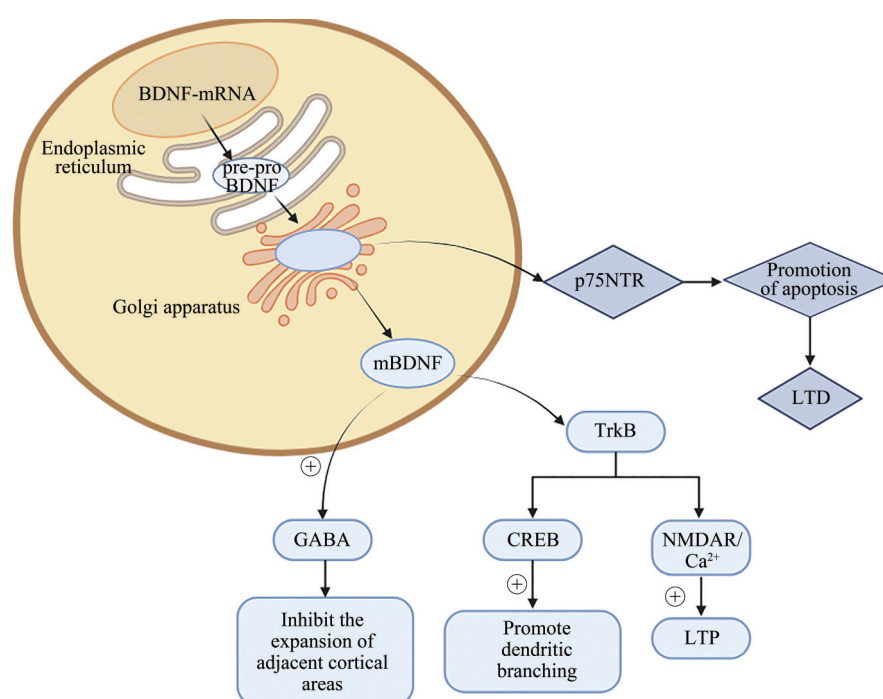
The Influence of BDNF on Cortical Remodeling After Peripheral Nerve Injury^{*}

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Graphical abstract



Abstract Peripheral nerve injury (PNI) severs peripheral connections and induces profound reorganization of primary somatosensory (S1) and motor (M1) cortical maps, a dynamic process that critically shapes the extent and quality of functional recovery. Brain-derived neurotrophic factor (BDNF) has emerged as a central molecular hub linking the initial peripheral insult to subsequent central plastic changes. This review systematically examines BDNF-mediated cortical remodeling following PNI, with a particular emphasis on its spatiotemporally specific regulatory mechanisms and the therapeutic opportunities they present. Immediately after PNI, deafferented cortical territories undergo rapid functional silencing and, over time, become progressively encroached upon by adjacent intact representations. This maladaptive reorganization—characterized by sensory map fusion and motor

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compensatory invasion—actively impedes successful reinnervation and optimal recovery. Such phenomena have been consistently documented in both non-human primate models and human fMRI studies, spanning sensory and motor modalities. Motor remapping is also prominently observed in facial nerve injury and chronic nerve compression models, underscoring the universality of these plastic changes. Notably, a range of interventions including regional local anesthesia, auditory-tactile substitution, and guided tactile imagery can effectively mitigate this aberrant remodeling, revealing promising avenues for the therapeutic modulation of cortical plasticity during critical post-injury windows. BDNF coordinates post-PNI cortical remodeling through three mechanistically interconnected pathways. First, BDNF drives dendritic and axonal growth *via* TrkB receptor signaling: retrogradely transported axonal signaling endosomes integrate CREB-dependent transcriptional programs with mTOR-mediated local protein synthesis to bolster dendritic arborization and axonal elongation, while BDNF-induced Limk1 translation precisely fine-tunes actin cytoskeletal dynamics, thereby stabilizing dendritic spine morphology. Second, BDNF governs GABAergic interneuron maturation and perineuronal net formation through the JNK signaling cascade, thereby acting as a “plasticity brake” that preserves the delicate excitatory/inhibitory balance and constrains indiscriminate, maladaptive rewiring. Third, BDNF robustly potentiates NMDAR-dependent long-term potentiation (LTP) by elevating NMDA channel open probability and increasing synaptic receptor density, thus tightly coupling structural remodeling with functional synaptic strengthening. Concurrently, long-term depression pathways are subject to modulation, with NMDAR antagonism exerting time-dependent, bidirectional effects that vary with the post-injury phase. Superimposed on these mechanisms, the functionally antagonistic actions of proBDNF/p75NTR (favoring pruning and growth cone collapse) and mature BDNF/TrkB (promoting survival and stabilization) add further layers of regulatory complexity, highlighting the absolute necessity for precise spatiotemporal control in any therapeutic strategy. Extending our previous experimental findings, we introduce a “cortical reclamation threshold” model. In this framework, early upregulation of BDNF-TrkB signaling enhances inhibitory tone to restrict cortical encroachment by neighboring intact regions, whereas delayed but precisely timed BDNF delivery following surgical nerve repair actively facilitates the reclamation of the original, deafferented cortical maps by regenerating afferent fibers. Importantly, the common BDNF Val66Met polymorphism may significantly modulate individual thresholds, providing a biologically grounded rationale for patient stratification and personalized timing of intervention. Despite this mechanistic promise, clinical translation faces considerable hurdles. These include inherently poor pharmacokinetics of BDNF, severely limited penetration across the blood-brain barrier, dose-dependent neurotoxicity mediated through the p75NTR receptor, and the overarching dual-edged nature of BDNF signaling, which can simultaneously promote both adaptive and maladaptive plasticity. Emerging delivery platforms—including engineered exosomes, polymeric nanoparticles, cryogel microcarriers, and adeno-associated virus (AAV)-based gene therapy—offer potential solutions, but all require rigorous pharmacokinetic, toxicological, and functional validation. Future research priorities should encompass: (1) comprehensive single-cell and spatial transcriptomic mapping to resolve BDNF cellular sources and real-time signaling dynamics across distinct cortical layers and cell types; (2) genotype-stratified dose-response studies to establish safe, effective, and personalized delivery protocols; and (3) large-scale multicenter clinical trials that seamlessly integrate BDNF-targeted interventions with multimodal rehabilitation strategies, such as repetitive transcranial magnetic stimulation and mirror therapy, with longitudinal neuroimaging serving as a biomarker for cortical reclamation. By systematically addressing these priorities, we aim to transform BDNF from a critical endogenous regulator into a precisely controllable and titratable therapeutic target, ultimately enabling a paradigm shift from mere structural repair to true functional neural reconstruction following PNI.

Key words peripheral nerve injury, cortical remodeling, BDNF, neuroplasticity, long-term potentiation

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