综述

神经调控技术在帕金森病治疗中的应用研究进展

胡灿芳[1,2]，钟传钰[3]，曹　立[1]

1. 上海交通大学医学院附属第六人民医院神经内科，上海 200233；2. 上海市第六人民医院金山分院神经内科，上海 201599；3. 上海交通大学医学院附属第六人民医院超声医学科，上海 200233

［摘要］帕金森病（Parkinson's disease，PD）是一种常见的神经系统退行性疾病，以静止性震颤、运动迟缓、肌强直、姿势异常为主要临床特征。多巴胺能药物是治疗PD的主要药物，但长期使用会使患者出现药效减退，甚至发生异动症、“开-关”现象等不良反应。神经调控技术是一种通过电能、磁场、超声等方式来兴奋或抑制大脑神经元活动、调节神经可塑性变化，从而达到治疗、改善疾病的生物医学工程技术。在PD的非药物治疗方面，神经调控技术作为一类新型的治疗手段，显示出了良好的疗效并具有不良反应少、易耐受等优点。基于此，该文针对脑深部电刺激、经颅磁刺激、经颅直流电刺激、经颅聚焦超声等常见神经调控技术在PD治疗中的应用研究进展进行综述。

［关键词］神经调控技术；帕金森病；脑深部电刺激；经颅磁刺激；经颅直流电刺激；经颅聚焦超声

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Research progress of neuromodulation in the treatment of Parkinson's disease

HU Canfang[1,2], ZHONG Chuanyu[3], CAO Li[1]

1. Department of Neurology, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200233, China; 2. Department of Neurology, Jinshan Branch of Shanghai Sixth People's Hospital, Shanghai 201599, China; 3. Department of Ultrasound Medicine, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200233, China

[Abstract] Parkinson's disease (PD) is a common degenerative neurological disorder, characterized by static tremor, bradykinesia, myotonia and postural abnormalities. Dopaminergic drugs are the main drugs in the treatment of PD, but long-term use will lead to drug efficacy loss, and even cause some adverse reactions such as dyskinesia and "on-off" phenomenon. Neuromodulation is a kind of biomedical engineering technology that can stimulate or inhibit the activity of brain neurons and regulate the changes of neuroplasticity by means of electric energy, magnetic field, ultrasound and other methods, so as to achieve treatment and improvement of diseases. In the non-drug treatment of PD, neuromodulation, as a new therapeutic means, has shown good efficacy, and has the advantages of small adverse reactions and easy tolerance. Based on this, this article reviews the research progress of several common neuromodulation in PD, including deep brain stimulation, transcranial magnetic stimulation, transcranial direct current stimulation and transcranial focused ultrasound.

[Key words] neuromodulation; Parkinson's disease (PD); deep brain stimulation (DBS); transcranial magnetic stimulation (TMS); transcranial direct current stimulation (tDCS); transcranial focused ultrasound (tFUS)

帕金森病（Parkinson's disease，PD）是一种以老年人发病为主的神经系统退行性疾病，临床上以静止性震颤、运动迟缓、肌强直和姿势步态异常等运动症状为主要特征，可伴有嗅觉减退、情绪情感障碍和睡眠紊乱等非运动症状；其主要病理改变为黑质多巴胺能神经元的大量变性丢失致纹状体多巴胺减少[1]，可引起PD相关的皮质基底节神经环路异常。目前，临床上常采用多巴胺能药物对PD进行治疗[2]；但随着病情进展该药物的疗效会逐渐减退，大部分PD患者于晚期出现严重的运动并发症，如异动症、“开-

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[作者简介]胡灿芳（1986—），女，主治医师，硕士生；电子信箱：tian2008shi2004@163.com。
[通信作者]曹　立，电子信箱：caoli2000@yeah.net。
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[Corresponding Author] CAO Li, E-mail: caoli2000@yeah.net.

关”现象等[3]，严重影响其生活质量。

神经调控技术是一类通过电能、磁场、超声等物理方式来兴奋或抑制大脑神经元活动、调节神经可塑性变化，从而达到治疗、改善疾病的生物医学工程技术[4]；该技术已广泛应用于PD、癫痫、肌张力障碍、震颤、抑郁等神经精神疾病。目前，神经调控技术被分为侵入性和非侵入性两大类，前者以脑深部电刺激（deep brain stimulation，DBS）为典型代表，后者包括经颅磁刺激（transcranial magnetic stimulation，TMS）、经颅直流电刺激（transcranial direct current stimulation，tDCS）和经颅聚焦超声（transcranial focused ultrasound，tFUS）等；且不同的调控技术所作用的脑功能区域和核团有所区别，即DBS和tFUS主要作用于脑深部核团，而TMS和tDCS主要作用于大脑皮层。本文针对DBS、TMS、tDCS和tFUS这4种神经调控技术在PD治疗中的应用研究进展进行介绍。

1　DBS

1987年，BENABID等[5]首次将DBS用于治疗和改善PD的静止性震颤症状，并达到了与丘脑切开相一致的抑制震颤的效果。该刺激方式主要通过在脑部特定靶点植入电极并由其发放电脉冲刺激实现对异常神经环路的调控，以达到控制运动症状的目的。目前，有关DBS的作用机制尚不十分明确，有研究认为DBS可通过持续去极化来触发电压门控钠离子和钙离子通道的失活[6]、提高细胞外钾离子浓度[7]，并诱导释放抑制性神经递质γ-氨基丁酸[8]，以阻断病理信号的传递；同时，也有研究认为，DBS通过刺激神经轴突或树突后，可沿神经纤维顺向或逆向激活下游神经元以产生新的动作电位，从而使病理性神经环路正常化[9]。

研究[10]显示，DBS治疗PD的主要靶点有丘脑底核（subthalamic nucleus，STN）和苍白球内侧部（globus pallidus internus，Gpi）。STN-DBS可明显改善PD患者在药物“关”期的运动症状，减少术后多巴胺药物的使用剂量[11]。对于由左旋多巴诱导的异动症（L-dopa induced dyskinesia，LID），STN-DBS可大幅降低患者的多巴胺能药物用量，而Gpi-DBS则可在不调整药物剂量、刺激强度的情况下直接改善LID的症状[12]。因此，Gpi-DBS对LID的直接抑制作用优于STN-DBS，尤其在需要维持高剂量药物的患者中获益更大[13]。在冻结步态治疗方面，Gpi-DBS主要可提高患者的步速，而STN-DBS则以增加步幅为主[14]。接受STN-DBS治疗的PD患者，其认知功能、情绪和语言流畅性等均受到较显著的影响，而由Gpi-DBS治疗引起的认知障碍、抑郁等不良反应相对较少[15]。因此，对于合并有认知和精神障碍的患者，选择Gpi-DBS治疗更为合适。

除STN、Gpi这2个经典的靶点外，丘脑腹中间核（ventral intermediate nucleus，Vim）和脑桥核（pedunculopontine nucleus，PPN）亦是治疗PD的潜在靶点。Vim-DBS治疗以改善PD患者的震颤症状为主。与单侧Vim-DBS相比，双侧Vim-DBS对改善患者中轴震颤的效果更为显著，但对肌强直和运动迟缓无明显效果[16]，并可能会加重患者的步态和构音障碍等[17]。低频（20~25 Hz）DBS刺激PPN靶点可提高患者统一帕金森病评定量表总分、显著改善其在药物“开”和“关”期的步态障碍和姿势异常[18]；且有研究[19]显示，双侧PPN-DBS比单侧刺激更有效。虽然诸多研究表明PPN-DBS可用于治疗和改善PD患者的冻结步态[20-21]，但由于PPN确切解剖位置尚存在争议，植入电极时定位非常困难[22]，PPN能否作为治疗冻结步态的可靠靶点仍争议较大[23]。

目前，DBS治疗手段相当成熟，且已成为治疗中晚期PD患者的最佳选择。临床上，我们需全面综合评估PD患者的年龄、临床特征、合并症、经济条件、安全性等方面，选择最优靶点，从而提高患者的生活质量并减轻家庭及社会负担。

2　TMS

TMS由BARKER等[24]于1985年创立，是一种基于法拉第电磁感应科学原理，利用电流通过线圈在颅内聚焦产生感应磁场，引发神经元动作电位，从而影响大脑皮层兴奋性的神经调控技术[25]。根据刺激模式的不同，TMS可分为单脉冲刺激、双脉冲刺激和重复经颅磁刺激（repetitive transcranial magnetic stimulation，rTMS）。其中，rTMS的临床应用最广泛，起初主要用于神经精神疾病，如抑郁症、脑卒中。1994年，PASCUAL-LEONE等[26]首次将rTMS应用于PD治疗，结果显示，与正常对照组相比，rTMS治疗可显著改善PD患者的运动症状；且其作用机制被认为可能是，rTMS通过刺激大脑皮层来促进

神经营养因子的生成、增加单胺类神经递质的释放，从而调节直接通路和间接通路的兴奋性[27]。近年来，国内外已开展了多项采用rTMS治疗PD患者运动及非运动症状的临床研究[28-30]，且该刺激已成为治疗PD的一种重要的非药物手段。

2021年，王丽娟等[31]发布了《中国帕金森病重复经颅磁刺激治疗指南》，对PD不同症状的治疗靶点及刺激频率的选择进行了明确规定。该指南推荐：①高频rTMS刺激初级运动皮层（primary motor cortex，M1）区可改善PD患者的运动迟缓症状，但对其震颤症状的改善不明显；刺激M1区和辅助运动区（supple-mentary motor area，SMA）对PD冻结步态短期可能有效；刺激左侧背外侧前额叶（dorsolateral prefrontal cortex，DLPFC）或双侧M1区可改善PD患者的抑郁症状，而刺激双侧DLPFC可改善患者的焦虑症状。②低频rTMS刺激SMA可改善PD患者的姿势步态障碍，与是否使用抗PD药物无关。此外该指南还提及，目前针对高频rTMS治疗PD患者认知障碍的相关研究结果并不一致，如高频（25 Hz）rTMS刺激右侧DLPFC可能改善PD患者的执行功能[32]、刺激额下回可能有助于改善其额叶认知功能[33]；高频（5 Hz）rTMS刺激右顶叶皮层可能有助于提高其学习能力[34]；高频rTMS还可改善PD患者的睡眠质量[35]。

因此，在进行rTMS治疗前，临床医师应严格按照TMS的适应证及禁忌证，并结合指南和根据患者的临床症状来制定个体化的最佳方案，以达到最优的治疗效果。

3 tDCS

tDCS是一种利用恒定、低强度的直流电（1~2 mA），通过头皮表面的阴阳电极来激活大脑皮层的静息膜电位，进而调节神经元电活动的技术；该技术具有安全、无创、损伤小等优点[36]，其作用机制与调节静息态神经网络功能连接[37]、改变大脑皮层兴奋性[38-39]和局部脑血流[40]、调节突触可塑性[41]等方面有关。

目前，采用tDCS治疗PD患者运动症状（如运动迟缓、姿势障碍）的常用靶点有M1区、DLPFC、SMA以及小脑。POL等[42]对18项随机对照试验进行meta分析，提示tDCS在改善PD患者姿势步态障碍和LID等方面有较好的作用。DAGAN等[43]对20名PD冻结步态患者给予不同模式的tDCS（即刺激M1区、M1和DLPFC双靶区、假刺激），刺激间隔至少48 h；结果显示，与刺激M1区和假刺激相比，刺激双靶区的患者冻结步态激发测试评分更低、步态速度更快、起立行走时间更短、Stroop干扰测试量表评分更高，表明联合靶区刺激可减少患者的冻结步态，并改善其执行和移动功能。另一项随机对照研究[44]中，LEE等在进行视觉提示下的步态训练之前对SMA予以阳极tDCS；结果显示，同未刺激组相比，tDCS组在达到同样的治疗效果时所需要的时间更短且效果更持久。FERRUCCI等[45]用阳极tDCS对PD患者的双侧小脑和M1区刺激治疗5 d后发现，其LID症状得到了显著改善，且BENNINGER等[46]研究也得到了类似的效果。

此外，采用tDCS治疗PD患者非运动症状（如认知、睡眠障碍等）的主要靶点有DLPFC和前额叶。CAMMISULI等[47]研究发现，对DLPFC进行阳极tDCS可增加刺激脑区局部皮质的兴奋性，从而改善PD患者的认知功能（主要为执行功能、语言流利度和工作记忆）。DORUK等[48]对PD患者的双侧DLPFC进行2周阳极tDCS，结果发现在1个月的随访中阳极tDCS组患者的执行功能比假刺激组有持续改善；该结果提示DLPFC的阳极tDCS对PD患者的执行功能有长期影响，可能与tDCS引起突触可塑性的长期变化有关。随后，有研究[49]对PD患者双侧前额叶和DLPFC进行1.2 mA的阳极tDCS，结果显示患者的帕金森病睡眠量表评分、睡眠潜伏期和总睡眠时间均有显著改善。此外，对左侧DLPFC行阳极tDCS亦可改善PD患者的疲劳，且疗效可持续至少3个月，但对改善其日间嗜睡无效[50]。

4 tFUS

2020年，SERVICK[51]指出超声治疗在脑部疾病中具有广阔的应用前景，能够安全且可预测地调控大脑功能。聚焦超声作为一种传播波，可以穿透包括颅骨在内的生物组织，其能量能够集中到一个微小的、有界的区域[52]，从而对细胞和组织产生热效应[53]和非热效应[54-56]，后者则主要分为机械作用、辐射力和空化效应共3种方式。tFUS是一种结合高穿透性和高空间分辨率的无创神经调节技术，可靶向刺激大

脑深部的功能核团，具有高度的空间特异性，同时对其他区域的影响较小[57-59]。根据强度的大小，tFUS可分为高强度聚焦超声（high-intensity focused ultrasound，HIFU）和低强度聚焦超声（low-intensity focused ultrasound，LIFU）[57]。SCHLESINGER等[60]使用一种HIFU即磁共振引导聚焦超声（magnetic resonance-guided focused ultrasound，MRgFUS）治疗难治性震颤型PD患者，结果显示该类患者的震颤症状得到了明显改善。而另一项使用MRgFUS对30例患者（包括18例特发性震颤患者、9例PD患者、3例PD合并特发性震颤患者）行丘脑毁损术的研究也获得了相同的结果[61]。MARTÍNEZ-FERNÁNDEZ等[62]将40例运动症状显著不对称的PD患者随机分为试验组（27例）和对照组（13例），采用HIFU靶向STN核团行单侧丘脑下毁损术，结果发现试验组患者症状严重的一侧肢体的运动症状得到了明显改善，其中震颤和肌强直的改善比运动迟缓更为明显。

近年来，我国也开展了较多采用HIFU治疗PD的临床研究。2022年，CHEN等[63]选取3例震颤型PD患者，在MRgFUS引导下对Vim和苍白球丘脑束进行双靶点刺激，结果发现治疗后1 d患者的震颤、僵硬、姿势异常均得到了明显改善，在随后1个月的随访中其症状的改善持续存在。该研究是我国首次采用双靶点进行HIFU治疗PD的临床研究，后续HIFU技术或将通过多学科协作被更广泛地应用于PD治疗。

相较于HIFU的毁损性和不可逆性，LIFU利用低强度超声的非热效应使神经元可逆地发挥兴奋或抑制作用，且不会对组织造成永久的热或机械损伤[56]，从而起到神经保护的作用。LIFU可通过减少细胞凋亡、诱导脑源性神经生长因子产生，显著改善PD模型小鼠的运动功能[64]。XU等[65]发现，利用低强度超声刺激PC12细胞和PD模型小鼠能诱导多巴胺的释放，并认为LIFU与神经元再生、超声机械力改善膜通透性有关。因此，LIFU被视为是一种较具潜力的治疗PD的无创神经调控方法[66]。

5　总结与展望

综上，神经调控技术作为一类新型的治疗措施，能够调控异常的神经环路，增加脑内血流量，促进脑内代谢和脑功能恢复，从而改善PD患者的运动症状和非运动症状。

值得注意的是，临床常用于PD治疗的神经调控技术（DBS、TMS、tDCS和tFUS）仍有一些实践相关的问题需要考虑，如治疗靶点、刺激参数（强度、时间、频率等）的选择。未来，我们将继续深入开展PD相关的基础及临床研究，探究其作用原理、调控靶点及刺激模式，并寻找新的治疗方法，从而为PD的神经调控治疗提供新的思考。

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HU Canfang was responsible for literature search and thesis writing. ZHONG Chuanyu participated in article revision. CAO Li was responsible for guiding article writing and participated in paper revision. All the authors have read the last version of paper and consented for submission.

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