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# 物理疗法在脑科疾病中的前沿应用: 神经治疗学的复兴

路翰娜[1,2,3*], 陈秀雯[2,3], 林翠华[2,3], 郑柏荣[4], 陈伟智[4], 何红波[1], 赵素华[1], 宁玉萍[1]

1. 广州医科大学附属脑科医院, 广州 510370;
2. 香港中文大学医学院精神科学系神经调节实验室, 香港 999077;
3. 香港中文大学医学院陈慧慧基金身心认知运动中心, 香港 999077;
4. 香港大学医学院精神科学系, 香港 999077
* 联系人, E-mail: hannabrainscience@gmail.com

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**摘要** 神经系统疾病在全球疾病负担和致残率的排位中居高不下, 但对其致病机理与个体化治疗方案的研究却较为局限. 从生物能量学的视角, 神经精神疾病涉及脑能量/代谢(例如熵)的异常. 在物理学中的电、磁、光、波为4种常见的能量形式, 而基于这4种能量形式的神经调控技术不仅在脑科学研究中占有重要一席, 同时也在脑科疾病的治疗中逐渐成为非药物治疗的重要方法. 本综述旨在介绍基于电、磁、光、波4种能量存在方式的神经调控方法在脑科疾病的前沿研究、技术难题与未来应用前景.

**关键词** 神经调控, 经颅电刺激, 经颅磁刺激, 深部脑刺激, 个体差异, 神经可塑性, 复原力

据2017年世界精神卫生组织报告, 在发达国家, 诊治精神疾病的花费占国民生产总值的3%~4%[1]. 在亚太地区, 这一个指标亦逐年上升, 尤其是随着社会发展与人口快速老龄化, 认知功能障碍与情感性疾病的发病率快速上升[2]. 面对如此严峻的形势, 尽管药物治疗发挥着重要作用, 但其在阿尔茨海默病、难治性抑郁症、重症强迫症和帕金森病(Parkinson's disease, PD)等大型临床试验中的治疗效果不佳, 且易出现代谢失调、消化道刺激等副作用. 例如STAR*D研究发现重症抑郁症患者中约有30%对药物治疗无反应或出现严重副作用[3]. 因此, 寻找并优化脑科疾病的替代性疗法逐渐成为临床神经科学的重中之重, 特别是以脑刺激(brain stimulation)为代表的神经治疗学(neurotherapeutics). 值得注意的是, 随着美国脑计划(BRAIN Initiative)、欧洲脑计划(Human Brain Project)、连接体(Connectome) 等一系列脑科学项目的开展[4], 人类对脑结构和功能的认识也不断加深, 尤其是疾病特异性脑网络的研究, 例如ENIGMA[5]和ADNI[6], 已较好地描绘出健康人和脑科疾病患者的脑网络特征, 而这也为寻找疾病相关的脑刺激靶位提供了影像学证据. 在理解神经环路的基础上, 脑刺激是通过对特定脑区的电场或磁场的调控达到缓解精神神经症状和提升认知功能的物理方法[7]. 本综述在介绍神经治疗学发展轨迹的基础上, 总结其在脑科疾病中的前沿应用与发展趋势.

## 1 非侵入性脑刺激

### 1.1 电休克与磁休克

电休克治疗(electroconvulsive therapy, ECT)是通过电流刺激大脑而引起皮层广泛性放电、意识丧失和全身抽搐以达到快速控制精神症状的治疗方法. 20世纪初ECT由意大利神经科学家Ugo Cerletti和Lucio Bini首次用于精神疾病治疗并发现ECT伴随严重的

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肢体痉挛和记忆障碍. 针对这两项副作用, Bennett和Liberson先后使用南美箭毒作为肌肉松弛剂以降低治疗中产生的强直痉挛, 以及使用短脉冲电流以减少ECT对记忆功能的损伤. 在此基础上, Holmberg和Saltzman通过改善肌肉松弛剂的给药途径, 使ECT更加安全[8]. 改良型电抽搐治疗在电抽搐治疗前用静脉麻醉剂和肌肉松弛剂, 并在脑影像的基础上使用微电波抑制大脑异常电活动, 不良反应明显减少.

磁休克(magnetic seizure therapy, MST)利用磁场产生高强度的脉冲磁场作用于大脑皮层区域, 产生的感应电流可干预神经元的电活动, 以此达到治疗疾病的目的. 在近年的临床应用中, MST刺激诱发的抽搐与ECT类似, 但持续时间较短, 发作时脑电图(EEG)波幅和发作后抑制更小, 能达到与ECT同样的抗抑郁效果. 2011年Kayser等人[9]通过比较MST与ECT, 发现两者在诱发抽搐时的电生理活动、肌肉收缩、EEG波幅和肌电图特征方面并无显著差异, 但经MST治疗的患者自主呼吸恢复和定向力恢复时间较ECT明显缩短.

### 1.2 经颅磁刺激

经颅磁刺激(transcranial magnetic stimulation, TMS)由Barke在1985年首次应用. 通过将绝缘线圈放在头颅特定部位, 当TMS的电容器放电时, 电流通过线圈并在线圈周围产生1.5~2.5 T的局部磁场, 这个磁场会以与线圈垂直的方向透过头皮和颅骨, 达到皮层表面以调节神经元的功能[10]. 依据刺激频率的差异, 低频TMS刺激(≤1 Hz)通过抑制局部神经元的活动, 降低大脑皮层兴奋性; 而高频TMS刺激(≥3~5 Hz)通过易化局部神经元的活动, 提高大脑皮层兴奋性[11]. 基于上述原理, TMS既是探索脑功能的工具, 也是重塑脑网络、治疗脑科疾病的方法. TMS应用于注意等认知功能和皮层可塑性的研究已有20多年的历史. 例如TMS作用于特定脑区可导致短暂的虚拟损伤, 即TMS相关的功能缺损图谱[12], 用来研究健康和患病人群的皮层特定功能与偏侧化. 随后Kossylin等人将TMS与任务执行实验相结合, 使用低频重复经颅磁刺激(repetitive TMS, rTMS)降低靶区域的血流, 同时也能减少与该区域相关的执行能力[13]. 这种技术在视觉成像与抑郁症的功能成像研究中亦起到重要作用.

在治疗方面, 自2008年TMS经FDA批准用于抑郁症的治疗后, 不同靶位与刺激方案的结合应用于不同疾病的治疗. 例如低频rTMS作用于补充运动区域(SMA)可有效缓解帕金森患者的不自主运动[14]. 而短阵快速脉冲TMS, 即持续$\theta$爆发式刺激, 在重症抑郁症的短程治疗中显现出可靠的治疗效果[15].

值得注意的是, 既往TMS的定位多数取决于治疗者的个人经验或依据10/20 EEG定位技术[16], 因此操作者之间差异(inter-performer variability)是一个不容忽视的问题, 而个体头颅的变异性和年龄或疾病相关的脑体积变化[17]亦会增加治疗效果的不确定性. 近年来TMS与MRI, PET, EEG的结合不仅加强了TMS的特异性, 也提升了TMS操作中的定位精准度. 基于脑网络导航的TMS也为神经网络模型、干预效果评估提供了更为宏观的视角[18].

传统TMS的局限性表现在: (1) 穿透力的局限: TMS穿透力约在2~3 cm, 即为皮层灰质或灰质白质交界处, 然而这一穿透力在脑萎缩的脑科疾病/老年群体中是不足的. (2) 占据大量医疗资源: 依照FDA推荐的方案, 每位患者的TMS治疗需要每周连续5次、30 ~ 45 min/次、连续3~4个星期. (3) TMS的安慰剂效应[19]. 鉴于上述局限, 近年发展出深部经颅磁刺激(deep TMS, dTMS)使用H型线圈, 刺激穿透力可达到6 cm, 可刺激到皮层下结构和深部脑纤维连接, 例如奖赏网络, 默认网络等[20].

### 1.3 经颅电刺激

经颅电刺激(transcranial electrical stimulation, tES)通过在头颅表面的导电贴板向脑内传递低强度电流(1~2 mA), 以达到提高或降低神经元的兴奋性来调控脑区的活动. 在古罗马时期, Scribonius Largus医生利用电鳐放电刺激患者前额部以缓解剧烈头痛, 由此发现电刺激对脑科疾病的治疗作用, 称为“脑极化”[21]. 依据传递电刺激的频率与模式的差别, tES主要有4种: (1) 经颅直流电刺激(transcranial direct current stimulation, tDCS); (2) 经颅交流电刺激(transcranial alternating current stimulation, tACS); (3) 经颅随机噪声刺激(transcranial random noise stimulation, tRNS); (4) 经颅脉冲电刺激(transcranial pulsed current stimulation, tPCS).

其中多数研究集中在tDCS和tACS. 3种常见的刺激方案: 正极刺激(anodal)、负极刺激(cathodal)和虚拟刺激(sham). 正极刺激增强神经元的兴奋性, 产生长期增强效应(LTP); 负极刺激抑制神经元的兴奋性,

产生长期抑制效应(LTD); 虚拟刺激为一种对照, 产生安慰剂效应[22]. 早期tDCS研究采用低电流密度(0.02~0.5 mA), 但由于缺少标准化方案, 不同研究间的结果差异很大. 随着临床试验不断开展, tDCS的治疗方案也不断规范化. 2006年首个双盲随机对照试验发现刺激左侧背外侧前额叶(DLPFC)可缓解抑郁症患者60%~70%的症状[23]. 在2008年另一项研究发现, tDCS对抑郁症状的改善可以维持30 d左右[24], 并且对提高老年抑郁症的反应率和降低复发率方面均有良好表现[25].

与tDCS不同, tACS通过变频电流调控目标神经元兴奋与抑制的阈值以达到改变皮层神经元的震荡节律. 依据EEG或脑磁图(MEG)的测量, 脑皮层的震荡节律可以划分5个波段, 即$\delta$(1~3 Hz)、$\theta$(4~7 Hz)、$\alpha$(8~13 Hz)、$\beta$(14~30 Hz)和$\gamma$(>30 Hz). 研究表明, 20 Hz的tACS可特异性影响β波段频率以实现对运动网络的调控[26]; 而高频tACS (AM-tACS)通过对α波段频率的影响以达到对听觉、视觉、体感等内源性系统的调控[27]. 相较于传统的tACS, AM-tACS可较好地分离EEG或MEG的噪音, 并且减少皮肤的不适感.

### 1.4 经颅超声刺激

经颅超声刺激(transcranial focused ultrasound stimulation, tFUS )是利用压力波的高穿透性, 刺激或者抑制大脑特定区域内神经元活动. 与TMS相似, tFUS包括低频和高频两种模式, 低频超声(0.5 MHz)能更好地穿透颅骨, 而高频超声具有更好的空间精确性, 例如0.5 MHz精确到3 mm, 而100 MHz可以精确到15 μm. 动物实验表明, tFUS的刺激深度可达海马区, 在低频刺激下可调控血脑屏障的开启与闭合, 并不会造成组织的损伤[28]. 目前关于tFUS的临床应用仅限于特发性震颤等少数几种疾病, 且报道较少. 在2017年发表的综述中FUS作为一种新的非侵入性脑刺激方法, 可用于不适宜外科手术的患者, 例如阿尔茨海默病和帕金森病[29,30]. 随着tFUS技术的不断优化, 在中高频(650 kHz)换能器的协助下, tFUS的精确度可达2 mm, 并可完成即时的临床反馈; 另外, 在MRI导航下, 低频(220 kHz)换能器与微泡协作完成阿尔茨海默病或者脑肿瘤患者的靶向给药.

### 1.5 经颅近红外激光刺激

光, 作为能量的一种, 在经颅近红外激光刺激(transcranial infrared laser stimulation, TILS)中透过颅骨作用于大脑皮层的神经元. 其治疗机制源于生物能量学: 低频的近红外激光作用于细胞膜以调节神经元的活动, 进而产生提升认知功能和治疗情感性疾病的作用[31]. 2013年首个随机对照试验证实TILS作用于DLPFC的对持续性注意、情绪控制能力均有提升效果[32]. 同理, 低能量红外光调节(photoneuromodulation)通过照射红外光, 使神经元内特定分子吸收光子以激活细胞信号传导通路, 尤其是线粒体内膜的细胞色素氧化酶的ATP代谢通路[33].

## 2 侵入性脑刺激

### 2.1 深部脑刺激

深部脑刺激(deep brain stimulation, DBS)的刺激位点为皮层下脑结构或核团, 需要开颅手术将电极植入脑内以传递低量的外源性电刺激. 在1950年DBS首次应用于帕金森病(PD)患者[34], 在2002年经FDA批准用于缓解PD患者的运动症状. DBS对PD的适应症包括以下几点[35]: (1) 原发性PD患者病情曾被药物治疗控制, 但疗效逐渐下降; (2) 异动症: 剂峰异动或双相异动症; (3) 药物难治性震颤; (4) 运动波动: “开-关”现象; (5) 肌张力障碍; (6) 无法耐受左旋多巴等抗帕金森病药物的不良反应(如药物诱发的直立性低血压). 由于PD是慢性脑科疾病, DBS手术的时间窗是影响疗效的重要因素. 有研究表明, PD合并轻度运动障碍的患者在术后两年的随访中生活质量优于单纯药物治疗的患者[36]. 当PD患者出现严重的中线症状(例如步态障碍、吞咽功能障碍)以及严重认知障碍或神经精神症状时, 提示DBS手术治疗的时间窗终点.

根据PD患者最为显著的症状选择刺激的部位, 较为多见的靶位有:

(1) 下丘脑核团(subthalamic nucleus, STN): 传统的恒频刺激针对步态障碍, 术后可减少左旋多巴用量30%~50%, 亦可以间接改善异动症[37], 但对震颤和僵直控制不佳. 近年发现变频刺激(variable frequency stimulation, VFS)作用于STN对于改善冻结步态和运动症状具有显著效果[38]. (2) 内侧苍白球(GPi): 针对运动迟缓、肌强直和震颤等症状, 有直接抗异动症的作用, 术后认知障碍的风险较小. 但不能减少左旋多巴的用量[39]. (3) 脑桥核(PPN): 对STN和

GPi治疗效果不佳的中线症状和步态障碍可能有效，但由于研究相对较少，结果尚存在争议[40]. (4) 丘脑腹中间核(vim): 只针对震颤症状，不能改善其他症状. (5) Meynert基底核: 低频刺激可改善精神症状，但对于认知功能的改善不显著[41].

除PD外，2009年FDA批准DBS用于强迫症的治疗. 在难治性抑郁症治疗方面，DBS尚处于试验阶段，且具有较大的争议性. 例如早期DBS选择刺激伏隔核(nucleus accumbens, NAcc)以缓解10例难治性抑郁症患者的抑郁焦虑症状[42]，研究发现，刺激伏隔核会引起扣带回膝部和前额叶区域的代谢，而这一结果也提供了新的刺激靶位. 在一项为期24周的DBS单盲安慰剂对照试验中，10例重症抑郁症患者和7例双相障碍患者接受扣带回膝部的DBS治疗，在随访中发现治疗后24周复发率为18%，应答率为41%；治疗后1年复发率为36%，应答率为36%；治疗后两年复发率为58%，应答率为92%[43]. 最近一项开放标签的临床试验尝试刺激背腹侧纹状体以治疗药物抵抗性抑郁症，经过16个星期的DBS治疗后并没有发现显著的改善[44]. 另外，相较于既往的开放环路DBS，闭合环路(closed-loop) DBS可以实时接收癫痫患者的状况并及时调整刺激参数，因此在癫痫症状控制方面更为高效[45].

### 2.2 迷走神经刺激

迷走神经属于颅神经，是自主神经的一种，主司副交感神经，控制气管收缩、心脏节律、腺体分泌、内脏分泌和收缩等运动的协调. 迷走神经刺激(vagus nerve stimulation, VNS)治疗中枢神经系统疾病的构想由Jacob Zabarra在1988年提出，他假设刺激迷走神经可以“自下而上”地改变大脑内的电位从而缓解癫痫[46]. VNS需要在患者左侧锁骨下的皮下置入一个类似心脏起搏器的发电机，用一条导线连接至左侧颈部的迷走神经. 相较于DBS，VNS的副作用较少，以短暂性声音嘶哑、颈部/喉部不适为多见.

### 2.3 脑膜下皮层刺激

脑膜下皮层刺激(epidural cortical stimulation, ECS)刺激特定脑区的硬脑膜，其作用方式更为直接；相较于DBS，ECS无须开颅手术更为安全[47]. ECS通过刺激改变电场的强度与方向，以此来调节神经元的电活动. 自2000年起，ECS被用于疼痛综合征、中风后康复、运动神经元疾病和PD的治疗[48]. 近年来，首个ECS治疗药物抵抗型抑郁症的随机对照试验($n$=5)发现在刺激左侧背外侧前额叶(DLPFC)后，患者的抑郁症状改善率在50%以上[49].

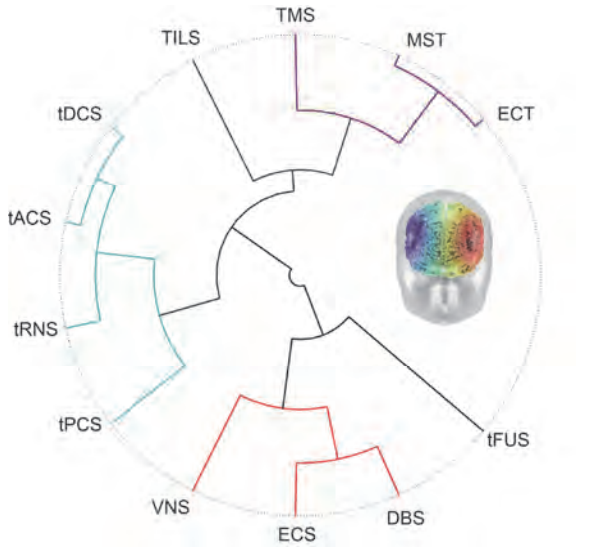


**图 1** (网络版彩色)神经调节技术的分类总结. TMS: 经颅磁刺激; ECT: 电休克治疗; MST: 磁休克; TILS: 经颅近红外激光刺激; DBS: 深部脑刺激; VNS: 迷走神经刺激; ECS: 脑膜下皮层刺激; tDCS: 经颅直流电刺激; tACS: 经颅交流电刺激; tRNS: 经颅随机噪声刺激; tPCS: 经颅脉冲电刺激; tFUS: 经颅超声刺激

**Figure 1** (Color online) The summary of modality-driven brain stimulation. TMS: Transcranial magnetic stimulation; ECT: Electroconvulsive therapy; MST: Magnetic seizure therapy; TILS: Transcranial infrared laser stimulation; DBS: Deep brain stimulation; VNS: Vagus nerve stimulation; ECS: Epidural cortical stimulation; tDCS: Transcranial direct current stimulation; tACS: Transcranial alternating current stimulation; tRNS: Transcranial random noise stimulation; tPCS: Transcranial pulsed current stimulation; tFUS: Transcranial focused ultrasound stimulation

## 3 神经调控术的难题与展望

多种神经调控技术在脑科疾病的研究和治疗中有着广泛的应用前景，但也存在亟待解决的难题. 第一，人群的高异质性(heterogeneity): 个体间的差异体现在易感基因、认知功能、脑结构等诸多方面. 其中与神经调控技术最为密切的参数之一，即颅骨-皮层距离 (scalp-to-cortex distance, SCD)，很大程度上影响电场/磁场在目标皮层的分布，但这一指标在年轻/年老，正常/脑科疾病人群中有着显著的差异. 第二，神经调控治疗的副作用报告与监控. 第三，治疗参数与疗效的可比性: 在了解异质性的基础上，临床对照试验的可比性、结果的可重复性亦是神经调控研

究的难点. 在未来的研究中, 将个体的临床资料、认知功能和基因特征构建成一个多维度的信息网络, 并通过这种信息网络支持精确诊断和个体化治疗. 在个体层面, 基因组、蛋白组、代谢组等分子数据, 认知功能、脑影像、神经调控治疗中的即时反馈等临床资料, 不同层级、不同维度的数据进行整合以确定个体健康状态和疾病转归. 从群体层面, 开放标签的多国/多中心合作对于统一疗效评估标准、提高研究结果可比性、达成参数设定共识等方面具有重要的意义.

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Summary for "物理疗法在脑科疾病中的前沿应用: 神经治疗学的复兴"

# Towards individualized psychiatric practice: The legacy of neurotherapeutics

Hanna Lu[1,2,3*], Sandra Sau Man Chan[2,3], Linda Chiu Wa Lam[2,3], Calvin Pak Wing Cheng[4], Wai Chi Chan[4], Hongbo He[1], Suhua Zhao[1] & Yuping Ning[1]

[1] *Guangzhou Brain Hospital, the Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou 510370, China;*
[2] *Neuromodulation Laboratory, Department of Psychiatry, the Chinese University of Hong Kong, Hong Kong 999077, China;*
[3] *Chen Wai Wai Vivien Foundation Therapeutic Physical Mental Exercise Centre, the Chinese University of Hong Kong, Hong Kong 999077, China;*
[4] *Department of Psychiatry, the University of Hong Kong, Hong Kong 999077, China*
* Corresponding author, E-mail: hannabrainscience@gmail.com

In 1997, Freeman Dyson postulated two categories of scientific revolution in his book *Imagined Worlds*. One kind is a concept-driven revolution, allowing us to explain "old things in new ways"; another kind is tool-driven revolution, allowing us to discover "new things that have to be explained". Twenty years later, this perspective still sheds new light on the emerging therapeutics in clinical practice. According to the annual report of the American Psychological Association (APA), prevalence of brain disorders is expected to rise tremendously over the coming decades. Taking dementia as an example, with rapid population aging in China, Alzheimer's Disease (AD) is expected to have profound impacts on the individuals and society. At present, there are no effective pharmacological treatments to halt or slow the progression of AD. Recent evidence found that non-pharmacological interventions, such as transcranial brain stimulation, are able to improve the cognitive functions and alleviate the psychiatric symptoms. However, given the limited studies, less is known about the underlying mechanisms and the potential tailored treatment with individualized features considered.

From the perspective of bioenergetics, brain disorders are due to the disturbance of metabolism or energy, such as entropy. One of the most profound links between metabolism and brain disorders is the dysfunction of mitochondria. Given the responsibility in producing ATP for energy, mitochondria use electrons and protons from molecular oxygen to reduce water and generate proton-motive force to produce ATP from ADP. Because the functioning of our brains only relies on the ATP mitochondria produced, thus when this process is impaired, a variety of brain disorders can occur.

From the perspective of physics, four types of energy, including magnetic, electricity, ultrasound and light, can be transformed to the cutting-edge stimulation technologies for exploring brain functions and enhancing the non-pharmaceutical therapeutics for brain disorders. In this review, we summarized the recent progress of the modality-driven brain stimulations and the state-of-art utility in psychiatric practice. The main interest will focus on the clinical applications of transcranial magnetic stimulation, transcranial electrical stimulation, transcranial focused ultrasound stimulation, transcranial infrared laser stimulation and deep brain stimulation.

Except for the empirical evidence, we will also point out the major limitations in the current brain stimulation studies. The framework comprises three innovative points: (1) Heterogeneity: Due to the heterogeneity within clinical population, causal inference with observational data in medical science is nearly impossible without strong assumptions. (2) Lack of key parameters: Scalp-to-cortex distance (SCD), as one of the most important and fundamental parameters of brain imaging and stimulation, has been highlighted in the newly updated guidelines. (3) Monitoring and reporting of the side effects induced by brain stimulation: several reports have mentioned the skin burns, pain and headache during the treatment of brain stimulation. However, we still have no standardized protocol to monitor and record the potential side effects. Taken together, this review introduces an in-depth understanding of the mechanisms of brain stimulation and its applications and future directions in individualized psychiatric practice.

**neuromodulation, transcranial electrical stimulation, transcranial magnetic stimulation, deep brain stimulation, heterogeneity, plasticity, resilience**

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