综　述

底丘脑核：从环路、功能到深部脑刺激治疗帕金森病的靶点

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摘　要：底丘脑核(subthalamic nucleus, STN)是基底神经节(basal ganglia)环路中唯一的兴奋性谷氨酸能核团，不仅是经典间接通路中的关键节点，而且接受皮层的直接投射从而构成超直接通路(hyperdirect pathway)，甚至被认为是驱动整个基底神经节活动的起搏器。STN由于其在基底神经节环路功能中的重要地位而成为临床上神经外科深部脑刺激(deep brain stimulation, DBS)治疗帕金森病(Parkinson's disease, PD)的首选靶区之一。尽管STN-DBS可显著改善PD运动障碍，但其发挥效应的神经机制至今不明。本文简要综述了STN的传入、传出联系及它们在基底神经节环路中的功能，特别讨论了STN-DBS改善PD运动障碍机制的假说和最新研究进展。我们认为，对STN-DBS作用机制的认识不仅有助于临床PD治疗策略的发展，也有助于对基底神经节环路功能的深入理解。

关键词：底丘脑核；基底神经节；运动控制；深部脑刺激；帕金森病；运动障碍

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Subthalamic nucleus: from circuits, functions to a deep brain stimulation target for the treatment of Parkinson's disease

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Abstract: The subthalamic nucleus (STN) is the only excitatory glutamatergic nucleus in the basal ganglia circuitry. It not only is a key node in the classical indirect pathway, but also forms the "hyperdirect" pathway directly connecting the cortex, and even is implicated as a pacemaker for activity of whole basal ganglia. Due to the key position of STN in the basal ganglia circuitry, the STN is an optimal target for deep brain stimulation (DBS) in the neurosurgical treatment of Parkinson's disease (PD). However, the therapeutic mechanisms underlying the amelioration of parkinsonian motor dysfunctions induced by DBS on STN remain enigmatic. This paper reviews recent progresses in the studies on the input-output configurations and functions of STN in the basal ganglia circuitry, and summarizes the hypotheses for mechanisms of DBS for the treatment of motor dysfunctions in PD. Studying on the DBS mechanisms will not only help to develop strategies for treatment of PD, but also contribute to the understanding of functions of the basal ganglia circuitry.

Key words: subthalamic nucleus; basal ganglia; motor control; deep brain stimulation; Parkinson's disease; motor dysfunctions

帕金森病 (Parkinson's disease, PD) 是基底神经节 (basal ganglia) 疾病谱上一种严重的神经退行性疾病。其临床表现不仅包括运动发起困难、肌肉僵直和静止性震颤等运动症状 (motor symptoms)，而且常常伴发睡眠紊乱及情绪情感障碍等非运动症状 (nonmotor symptoms)[1–3]。尽管距 1917 年 James Parkinson 首次描述震颤麻痹已近 200 年，人们对 PD 发生和发展的病理生理过程的认识和临床治疗策略的完善仍面临着许多亟待研究的重要问题。有趣的是，深部脑刺激 (deep brain stimulation, DBS) 作为临床神经外科治疗 PD 运动障碍一种非常有效的疗法[4, 5]，其确切的神经机制却至今不明，这也从一定程度上阻碍了 DBS 的推广和发展。本文即聚焦于 DBS 治疗 PD 中的首选靶区之一 —— 底丘脑核 (subthalamic nucleus, STN)，这一基底神经节环路中唯一的兴奋性谷氨酸能核团和关键节点，扼要综述和讨论 STN 在基底神经节环路中的功能和 STN-DBS 改善 PD 运动障碍的可能机制。

1 STN概述

STN 是位于大脑脚 (cerebral peduncle) 和未定带 (zona incerta) 之间的一个神经元十分密集且高度血管化的结构。因其周围被有髓鞘纤维束所包绕，因而被认为是一个"封闭的 (closed)"核团[6]。STN 神经元的胞体呈梭形、圆形、锥形或三角形，直径 25~50 μm 不等，内含丰富的细胞器，但粗面和滑面内质网的含量相对较少[7]。STN 中的主神经元 (principle neuron) 是长轴突的谷氨酸能投射神经元，但 STN 中是否存在中间神经元 (interneuron) 目前仍有争议[8]。形态学研究表明，尽管 STN 在大鼠、猫和猴等不同物种中大小各异，但其神经元的形态学特征和胞体 - 树突树的三维结构却非常相似[6,8]。

2 STN的传入传出联系

2.1 间接通路(indirect pathway)

间接通路和直接通路 (direct pathway) 共同构成了基底神经节中的两大经典环路，一般认为二者活动的平衡决定了基底神经节功能的正常执行。STN 作为间接通路中的关键节点 (图 1)，接受来自苍白球外侧部 (external segment of the globus pallidus, GPe) 的传入，并发出直接纤维投射到苍白球内侧部 (internal segment of the globus pallidus, GPi)，从而将间接通路 (纹状体 -GPe-STN-GPi) 与直接通路 (纹

状体 -GPi) 联系起来[9]。

免疫组织化学研究显示，GPe 神经元及其支配 STN 神经元的轴突末梢均表现出谷氨酸脱羧酶和 GABA 免疫阳性[10]，提示 GPe 向 STN 的投射是 GABA 能的。在哺乳动物脑内，GPe 向 STN 投射的空间拓扑关系是：GPe 腹侧部的神经元投射到 STN 喙外侧 2/3 部；GPe 最外侧部的神经元主要投射到 STN 喙端 2/3 部和中间 1/3 部；而 GPe 中间部的神经元则主要投射到 STN 外侧 1/3 部[9]。

神经解剖学及顺行示踪研究显示，STN 向 GPi 发出的直接的谷氨酸能神经纤维投射穿过内囊，进入 GPi 尾部，继而呈放射状支配苍白球各部，其中大部分投射纤维的走向均与内髓板平行[11]。实际上，除 GPi 之外，STN 还发出直接纤维投射至 GPe。顺行和逆行示踪研究表明，STN 向整个苍白球的投射呈反相背腹侧拓扑组构，即背侧 STN 更多地支配腹侧苍白球，而腹侧 STN 则更多地支配背侧苍白球[12]。从喙尾轴上看，STN 尾端和内侧部的细胞主要投射至 GPi，而 STN 喙端和外侧部则主要投射至 GPe[13]。因此，接受 GPe 传入的 STN 不仅支配 GPi 从而构成间接通路，而且与 GPe 之间存在双向的神经环路联系，这一联系很可能是 STN 与 GPe 作为整个基底神经节环路活动起搏器 (pacemaker) 的重要结构基础[14, 15]。

2.2 超直接通路(hyperdirect pathway)

大脑皮层对 STN 直接的兴奋性谷氨酸能神经纤维投射构成了基底神经节环路中的超直接通路[16, 17]，这一新近揭示的神经环路很可能在随意运动的发起、执行和终止中发挥重要作用。实际上，对啮齿类动物的研究早就表明，初级运动皮层、前额叶皮层部分区域、扣带回皮层的前区和中区、初级躯体感觉皮层和岛叶皮层等均有向 STN 的直接纤维投射[18]。这一超直接通路主要起源自皮层的第 V 层锥体细胞[19]，其向 STN 发出的含有球形囊泡的纤维末梢优先与 STN 神经元的树突形成非对称突触 (asymmetrical synapses)[14, 20]。猴的大脑皮层亦存在对 STN 的直接纤维投射，但这一直接投射在皮层中的起源区域及其在 STN 中的终止区域在不同物种间差异很大。例如，在猫猴 (owl monkey) 和恒河猴 (macaque monkey) 中存在的 8 区皮层向 STN 的直接投射在松鼠猴 (squirrel monkey) 中就不存在[21]。另外，对大脑皮层 -STN 直接投射的双侧性亦存在争议。有研究者认为，皮层对 STN 的投射
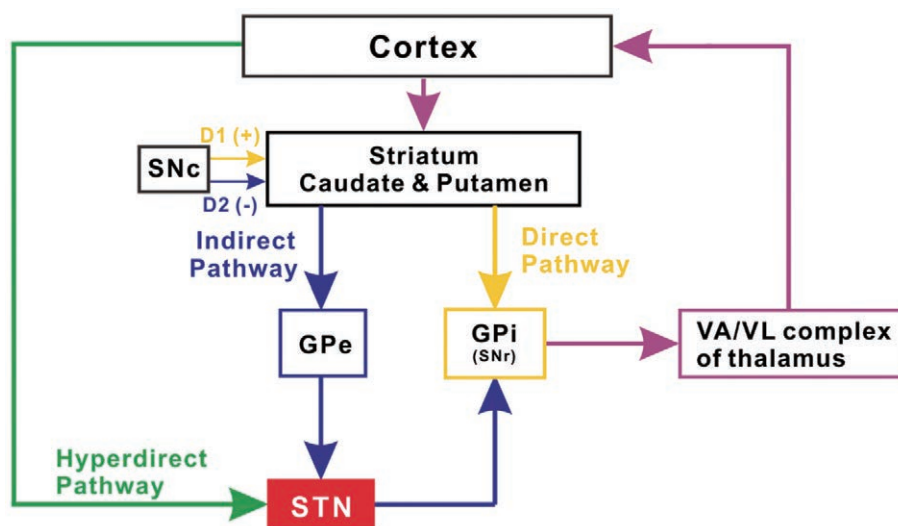
图 1. 底丘脑核与基底神经节直接通路、间接通路和超直接通路

Fig. 1. The subthalamic nucleus and the direct (yellow), indirect (blue) and hyperdirect (green) pathways in the basal ganglia. The cortico-subthalamo-pallidal 'hyperdirect' pathway conveys excitatory inputs from the motor-related cortical areas to the globus pallidus and holds a key position in a dynamical balance of basal ganglia circuitry with indirect and direct pathways. SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulate; GPe: external segment of the globus pallidus; GPi: internal segment of the globus pallidus; VA/VL complex: ventral anterior and ventral lateral complex; STN: subthalamic nucleus; D1, dopamine receptor D1; D2, dopamine receptor D2.

起源于整个大脑皮层且为双侧投射 [22]，而另有研究者则认为皮层对 STN 的投射仅局限于皮层的特定区域且为同侧投射 [23]。总的来说，皮层到 STN 背外侧部的纤维投射主要起源于初级运动皮层的 4 区 [24]，该投射能够在肢体运动和受到躯体感觉刺激时调节 STN 神经元的放电频率 [25]；而投射到 STN 腹内侧部的神经纤维则主要起源于初级运动皮层的 6 区及 8、9 区，这些区域主要参与视觉眼球运动及相关运动行为的控制 [26]。因此，STN 能够平行地接受来自大脑皮层的多重信息并传递给基底神经节 [27]。

2.3 其它传入传出神经联系

STN 除接受 GPe 和大脑皮层的直接神经纤维投射之外，还接受来自丘脑的投射。在哺乳动物，这些丘脑投射神经元仅局限于束旁核 [28]；而大鼠的丘脑 -STN 投射纤维起源于丘脑的一些特定亚区，并呈现对应的空间拓扑定位关系 [29]。顺行和逆行示踪研究显示，STN 还可接受黑质发出的直接神经纤维传入，并且 STN 神经元上有中等密度的多巴胺受体表达 [30]。此外，研究还显示 STN 神经元上有组胺和 orexin 等单胺类和神经肽类受体 mRNA 的表达 [31, 32]，提示 STN 可能还接受来自下丘脑和 / 或脑干的直接的单胺能和 / 或肽能纤维投射。

黑质网状部 (substantia nigra pars compacta) 是除苍白球之外接受 STN 投射最主要的靶区之一。神经环路示踪研究揭示，STN 到黑质的神经纤维投射呈拓扑组构 [33]。其中，绝大多数纤维直接投射到黑质网状部中的兴奋性谷氨酸能神经元，其余的神经纤维则跟随黑质致密部中的多巴胺能神经元一起上行进入黑质网状部。这些研究表明，STN 与黑质间存在非常紧密的双向神经纤维联系，STN 既可能调控黑质中的非多巴胺能神经元，也可能影响其中的多巴胺能神经元。

综上所述，STN 除了作为基底神经节中纹状体 -GPe-STN-GPi 间接通路和皮层 -STN-GPi 超直接通路中的重要节点之外，还接受来自丘脑的中央中核 / 束旁核复合体、下丘脑以及脑干中黑质、中缝背核、蓝斑等脑区的纤维投射。而 STN 发出的神经纤维除投射至 GPi 外，还投射至 GPe、黑质网状部、纹状体和脚桥核等核团。并且，STN 还与基底神经节中的 GPe 和黑质网状部间存在直接的双向环路联系。这些 STN 的传入传出联系成为 STN 神经元活动，特别是 STN 运动调控和非运动调控功能的神经解剖学基础。

3 STN 神经元的基本电生理学特征

STN 神经元有三种电活动模式：紧张性放电、

节律性爆发式放电和不规则放电[34-36]。其中，绝大多数 STN 神经元表现为紧张性放电 (80%~98%)，少数 STN 神经元表现为节律性放电和不规则放电[35,36]。值得注意的是，STN 神经元爆发式放电和不规则放电活动的显著增加可作为 PD 的特异性电生理学指标之一[37,38]。此外，约有 3.8% 的 STN 神经元表现出周期性振荡电位，且其与对侧肢体的肌电图有非常显著的同步性，称之为震颤细胞 (tremor cells)。这些细胞的放电频率为 23~88 Hz，平均为 (49.1 ± 15.2) Hz，略高于其它 STN 神经元的放电频率，亦为临床手术中定位 STN 的特征性标志之一[39]。此外，电生理学结合药理学研究显示，STN 神经元上存在钙激活钾通道、T/R 和 L 型钙通道以及超极化激活的环核苷酸门控 (hyperpolarization-activated cyclic nucleotide-gated, HCN) 通道等离子通道，这些离子通道的活动影响了 STN 神经元的基本电生理特性，也包括了自发放电频率及放电模式[40-43]。

4 STN在基底神经节环路中的功能

基底神经节环路对机体运动功能的调节具有非常重要的作用，包括随意运动的发起、肌紧张的控制、本体感觉传入信息的处理等，同时也参与了精巧运动的形成。除了经典的两条相互平行但功能对抗的直接通路和间接通路之外，来自大脑皮层向 STN 发出的超直接通路的功能近年来受到了越来越多的关注。STN 作为关键运动控制结构，参与的基底神经节中间接通路和超直接通路这两条抑制运动的通路与易化运动发起的直接通路之间的平衡，对整个基底神经节发挥正常的运动调控功能具有至关重要的作用。

4.1 STN在基底神经节躯体运动功能中的作用

在经典的间接通路中，STN 接受 GPe 的 GABA 能传入并发出谷氨酸能传出到 GPi，从而增强基底神经节向丘脑的抑制性输出，特异性地终止由直接通路激活所产生的运动[44-46]，实现了间接通路与直接通路间的平衡与基底神经节环路正常的运动功能。对大鼠的电生理学研究表明，在纹状体信号到达之前，STN 传出即可通过预先改变 GPi 和黑质网状部神经元的膜电位或通过对突触传递进行调节，使二者对来自纹状体的直接通路信号达到恰当的反应水平[47]。在人和猴，一旦 STN 出现损伤 (如出血或损毁)，便会导致偏身颤搐 (hemiballismus，即对侧肢体的不自主运动)；而损毁 GPi 后，这一症状便可消失。此外，因 STN 上游传入紊乱引起自身去抑制而增强间接通路向 GPi 的输出与 PD 患者的强直、运动迟缓、静止性震颤等运动症状的产生密切相关。因此，经 STN 的间接通路在 PD 中的活动增强成为临床神经外科手术损毁 GPi 以切断 STN 对其的兴奋性传入或对其施予 DBS 来治疗 PD 的理论基础[48,49]。

随着近年来大脑皮层到 STN 的谷氨酸能超直接通路的发现，研究揭示该通路的激活可引起 STN 神经元产生短潜伏期且强烈的兴奋性突触后电位 (excitatory postsynaptic potential, EPSP) 并抑制大鼠的运动行为[23,50]，提示超直接通路与经 STN 的经典间接通路一样均发挥了抑制运动的功能。研究表明，超直接通路能够先于直接通路的抑制信号发出前，将皮层的兴奋性输出信息经由 STN 发出的谷氨酸能投射纤维传递给基底神经节的传出核团[44]，以介导一个快的终止 / 暂停信号 (rapid stop/pause signal)[16,51]。在 PD 进程中，由于基底神经节失去黑质多巴胺能神经传入的动态调控，致使超直接通路和间接通路与直接通路之间的相对平衡被打破，并以超直接通路和间接通路的活动异常增强为显著特征，从而最终引起基底神经节环路的运动功能障碍[52,53]。

有趣的是，Plenz 等在对间接通路的研究时意外发现，STN 还很可能与 GPe 一同构成 GPe-STN 复合体，发挥基底神经节环路核心起搏器的作用[54]。STN 神经元膜上电压门控 Na$^+$ 电流的持续性激活[41,43] 和复活[55] 可以使 STN 神经元产生自发放电活动，从而通过其对基底神经节各结构的广泛支配驱动整个基底神经节的运动环路。在 PD 病理状态下，皮层对 STN 的兴奋性谷氨酸能神经传入可促使具有双向投射的 STN-GPe 复合体出现明显的共振 (synchronized oscillations)[54,56]，这也为揭示基底神经节环路在正常及病理情况下产生同步化振荡活动的神经机制提供了重要的线索。

事实上，大脑皮层能够通过异突触的方式调节 GPe 到 STN 的抑制性 GABA 能传入[20,53]。在 PD 模型动物中，GPe 对 STN 的抑制作用能够随着运动皮层的激活发生相位偏移 (phase-offset)。这很大程度上是由于纹状体向苍白球的抑制性 GABA 能神经传入的异常亢进引起的，并可能导致 STN 神经元电活动皮层模式 (cortical patterning) 的过度激活[57-59]。这些研究表明，由 STN 参与构成的超直

接通路和间接通路并非两条完全相互独立运行的运动控制环路。

4.2 STN在基底神经节非运动功能(情绪情感和奖赏)中的作用

基底神经节也参与了对情绪情感、奖赏和认知等非躯体运动功能的调控 [60–62]。对人和动物的研究表明，STN 在情绪和动机中发挥重要的调节作用 [63–65]，参与了情绪加工的不同阶段，如情绪认可和主观情感过程。Sieger 等 [66] 在对 PD 患者进行 DBS 治疗的过程中，通过记录单个 STN 神经元的放电模式发现，参与情绪效价 (emotional valence) 和唤醒度调节的神经元分属不同的 STN 细胞亚群，提示 STN 可能作为边缘系统的核心在情绪情感加工中发挥重要作用。另有证据显示，STN-DBS 可引起少数患者一过性的抑郁 [67]。并且，Voon 等通过对 PD 患者接受 STN-DBS 治疗后跟踪研究发现，患者术后一周内的死亡率虽为 0.4%，但其中部分为自杀所致 [68]。此外，在人类的 STN 中还存在参与视觉和情绪信息处理及传递的神经元 [26]。

另一方面，STN 在本能性奖赏行为中亦发挥重要作用。但有意思的是，STN 对摄食和药物滥用的调节作用似乎截然相反，即损毁双侧 STN 在提高摄食动机的同时，却降低了对可卡因的摄取 [65]。由于 STN 对药物滥用具有敏感性，所以重复给予可卡因导致 STN 代谢活动的降低，而 STN 损毁的大鼠在工作压力增大时表现出可卡因获取动机的下降 [69]。因此，STN 不仅作为基底神经节环路中的关键结构参与机体躯体运动功能的调控，也在基底神经节的非躯体运动功能中发挥重要的作用。

5 STN-DBS在PD临床治疗中的意义

5.1 DBS

在高频 DBS (> 100 Hz) 改善 PD 运动障碍这一疗法出现之前，缓减 PD 症状的途径主要包括药物治疗和外科手术损毁治疗两种。药物治疗主要针对 PD 患者黑质致密部多巴胺能神经元退变导致多巴胺水平下降而使用多巴胺的前体 —— 左旋多巴 (L-dopa) 或多巴胺受体激动剂 bromocriptine、pergolide 和 apomorphine 等 [48, 70, 71]，其中又以口服左旋多巴最为常用。虽然服用左旋多巴能够较快地改善 PD 症状，但长期使用则常常会产生药物依赖和异动症等副作用 [72, 73]。外科手术损毁疗法则基于经典的基底神经节直接通路和间接通路理论 (图 1) 提

出，考虑到 PD 病理进程中直接通路活动减弱而间接通路输出增强，因此选择间接通路的关键节点 STN 或两条通路会聚后向丘脑抑制性输出的最终节点 GPi 进行损毁 [71, 74]。损毁 STN 尽管能够完全永久地改善由 MPTP 诱导的模型猴的 PD 症状 [71]，但对于 PD 患者仅能在一定程度上缓解静止性震颤 [75]，却不能缓解其他运动症状，甚至可能引起部分症状的恶化 [76]。另一方面，由于损毁的不可逆性，其风险性很高。

自 1987 年起，Benabid 等首先对基底神经节 - 丘脑 - 皮层环路中的丘脑进行 DBS 治疗的尝试，并于 1993 年首次报道了 3 位 PD 患者在接受 STN-DBS 治疗后而显著改善了震颤、僵直以及运动徐缓等 PD 症状 [77](图 2)。随后，美国 FDA 于 1997 年起陆续批准 DBS 用于临床治疗 PD 等多种神经系统疾病，其安全性和疗效得到进一步的广泛认可。目前，临床 DBS 应用立体定位技术结合磁共振成像将微电极精确地植入患者 STN，并通过皮下植入式脉冲发生器对 STN 进行电刺激从而缓解中晚期，特别是晚期药物疗效甚微的 PD 患者的运动症状 [78–90]。有研究者甚至认为 DBS 是一种优于口服左旋多巴的疗法 [91]，且 DBS 除能够缓解 PD 运动症状之外，还能够缓解药物治疗 PD 引起的副作用 [73]。仅有一些研究报道 DBS 可能引起少数患者抑郁或出现认知障碍，例如冲动 [68, 92–95]。随着 DBS 在 PD 临床治疗中的广泛应用，除 STN 外，还有许多脑区也被尝试用做 DBS 治疗 PD 的靶区，如脚桥核、GPe、GPi 和黑质网状部等，但是刺激不同的脑区所使用的 DBS 刺激参数不尽相同 [73, 96–99]。此外，DBS 也被越来越多地用于治疗其他神经系统疾病，如刺激伏隔核、腹侧内囊、腹侧纹状体及苍白球等治疗难治性抑郁症 (treatment-resistant depression)、强迫性障碍 (obsessive-compulsive disorder)、原发全身性或节段性肌张力障碍等 [93, 100, 101]。

5.2 STN-DBS改善PD运动症状的可能机制

尽管 STN-DBS 用于 PD 临床治疗的有效性得到一致的认同，而无创性 DBS 技术 [102] 的问世势必进一步推动 DBS 的临床应用。但迄今为止，STN-DBS 发挥疗效的神经机制一直充满矛盾和争议 [78]。因此，准确、深入地理解 DBS 的神经机制愈发显得迫在眉睫。

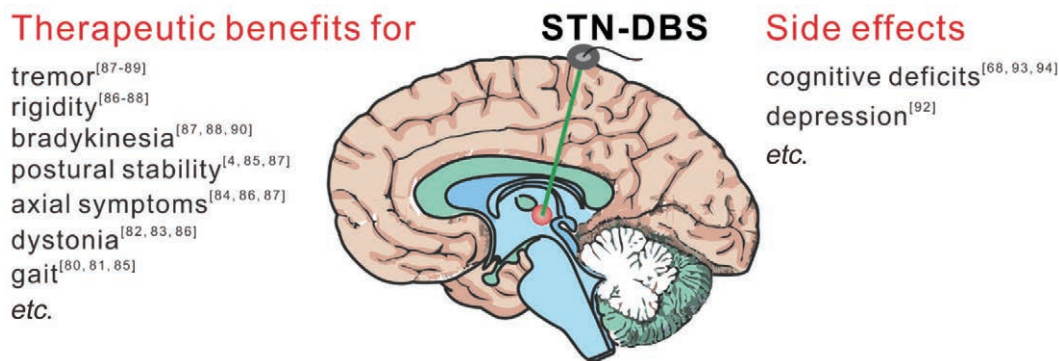早期的研究显示，PD 模型动物和 PD 患者中 STN 神经元的放电频率升高，呈过度兴奋状态 [37, 71, 103]，

图 2. STN-DBS的治疗效应与副作用

Fig. 2. Therapeutic benefits of subthalamic nucleus (STN)-deep brain stimulation (DBS) for the treatment of Parkinson's disease (PD) and its side effects. The numbers cited in superscript are the relevant references.

由此推测 STN-DBS 很可能是通过高频刺激压抑 STN 神经元活动导致基底神经节向丘脑的抑制性输出减弱，最终使得大脑皮层的兴奋性增加来发挥其作用。一些研究报道，对 PD 患者及 PD 模型大鼠施予 DBS 后，STN 神经元兴奋性降低[104–106]，这一压抑效应可能是通过 STN 神经元上钠离子通道的失活和钾离子通道电流的增加来实现的[107–109]。此外，也有研究者认为 STN-DBS 可能通过兴奋来自 GPe 的 GABA 能神经纤维末梢促进 GABA 的释放进而抑制 STN 神经元的活动[110]。

然而，DBS 抑制 STN 神经元活动的假说受到许多临床和实验研究的挑战。一方面，STN-DBS 并不显著降低 STN 神经元的电活动[111–113]；而另一方面，STN-DBS 反而使得 STN 投射靶区 GPi 神经元的电活动增加了[111]，且 PET 和 fMRI 研究均揭示了与神经元兴奋相一致的 GPi 血流量[114]和血氧水平[115]的增加。靶区神经元兴奋的现象明显与 DBS 抑制刺激位点神经元活动的假说相悖。因此有研究者认为，该矛盾可能是细胞外电刺激在激活抑制性突触前末梢从而抑制胞体本身的电活动的同时又激活轴突进而兴奋其靶区神经元的结果[116]。这一解释将刺激机制集中于传入和传出神经纤维而非神经元胞体，使得目前对 DBS 机制的认识逐渐从刺激靶点 STN 本身拓展到神经环路乃至神经网络的水平上，并发展出激活过路纤维和改变基底神经节 - 皮层神经环路 β 振荡两个优势假说。

近年来，许多研究者开始认为 STN-DBS 可能通过影响经 STN 的过路纤维[117]，特别是来自大脑皮层的超直接通路[67, 112, 117–120]而发挥效应。应用光遗传学技术的研究显示，仅仅特异性抑制或兴奋 STN 神经元并不改善 PD 模型大鼠和小鼠的运动障碍，而选择性激活过路纤维或初级运动皮层第 V 层锥体细胞则显著改善 PD 运动障碍[112, 121]，有力地佐证了 DBS 激活 STN 过路纤维的假说。

另一方面，还有研究显示，PD 病理进程中伴有 STN 乃至整个基底神经节局部场电位 β 同步化振荡 (10~30 Hz) 的增强[50, 122, 123]。STN 的 β 同步化振荡增强被认为是多巴胺水平下降后的继发表征之一，并且 STN 可以通过其与苍白球间双向联系构成的起搏器样复合体将这一 β 同步化振荡扩散至整个基底神经节环路[124, 125]，而该 β 同步化振荡与 PD 患者的运动徐缓和运动不能密切相关[90, 126]。与此相应的是，临床上观察到，在对 PD 患者施予 STN-DBS 改善运动症状的同时伴随有基底神经节 - 皮层环路 β 同步化振荡活动的减少[127–129]。并且，STN-DBS 对超直接通路的刺激可逆行激活运动皮层投射神经元产生逆行动作电位，抑制皮层的 β 同步化振荡，从而改善 PD 动物的运动障碍[130, 131]。此外，对 PD 患者施予 STN-DBS 后，亦可逆行兴奋皮层中间神经元，进而调节皮层 - 基底神经节 - 皮层环路的异常活动[132, 133]。

6 结语

综上所述，STN 作为整个基底神经节中唯一的兴奋性核团在基底神经节环路中发挥了十分关键的作用。其不仅构成了间接通路和超直接通路中的重要一环，而且支配了基底神经节环路中的其它结构从而发挥起搏器的作用。正基于此，STN 既在基底神经节躯体运动环路的随意运动发起、肌紧张控制、本体感觉传入信息处理和精巧运动形成中发挥重要

功能，亦参与了基底神经节非躯体性的情绪情感和奖赏调节。从整合生理学和整合神经生物学角度，对 STN-DBS 改善 PD 运动障碍神经机制的深入系统研究将对临床进一步优化 DBS 参数和 PD 治疗策略具有重要意义。

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