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Review Article

Deep brain stimulation for the heterogeneous pathophysiology of Parkinson's disease

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ABSTRACT

Deep brain stimulation affects the pathophysiology of various motor disorders including essential tremor, Parkinson's disease (PD) and dystonia. The motor deficits from PD have been explained by the firing rate and pattern models. However, due to the variability between patients' electrophysiology, the pathophysiology for PD is difficult to sparse apart. Neither model can fully explain the spectrum of patient presentations. The localisation and stimulation of various structures including the subthalamic nucleus, globus pallidus internus and ventral intermediate nucleus lead to different effects on the patient's motor symptoms. This group of targeted structures affects the models of PD in distinct ways. This review aims to explain the models of PD and the effects of stimulation in each structure.

Keywords: Parkinson's disease, Pathophysiology, Deep brain stimulation

INTRODUCTION

Deep brain stimulation (DBS) is an effective treatment for the motor symptoms of essential tremor (ET), Parkinson's disease (PD) and dystonia. The physiological structure of the lead location is the most important factor in determining the effects that stimulation will have on the patient. Three of the main structures that are targeted for lead implantation in PD DBS surgery are the subthalamic nucleus (STN), globus pallidus internus (GPi) and ventral intermediate nucleus (Vim). Several models of PD pathogenesis have been mapped out to understand the disease. While each model has unexplained components, they provide a template for the reasoning behind the location of DBS leads. Understanding the effects of implantation in certain structures is important to optimise the lead location for patients. The different pathways and mechanisms of DBS will be explored in this paper concerning their respective therapeutic effects.

CURRENT BASIC PARKINSONIAN PATHOGENESIS MODELS

Firing rate model

The basal ganglia are central to the motor circuit. Various factors determine the output of the basal ganglia.[1] Based on the firing rate model, in the normal state, the basal ganglia are controlled by a direct and indirect pathway. The indirect pathway inhibits the thalamus from sending messages to the cortex. This occurs by inhibitory signals from the striatum and decreased activity from the globus pallidus externus (GPe), which, in turn, increases STN activity. The STN

then sends excitatory messages to the GPi and increases the GPi inhibitory signals, which controls the thalamus.[2] On the other hand, the direct pathway disinhibits the thalamus from stimulating the motor cortex through excitation of the striatum, which inhibits the GPi inhibitory signals. This will allow for the initiation of movement.[1] The substantia nigra influences the pathways with an excitatory and inhibitory signal to the striatum in the direct and indirect pathway, respectively.

In the Parkinsonian model, the dopamine degeneration in the substantia nigra shifts the activity of the indirect motor pathway described above. The loss of the cells in the substantia nigra changes the indirect pathway and there is less inhibition of the striatum inhibitory activity.[1] This leads to the suppression of the thalamus-motor cortex network through the increased activity of the STN-GPi projection. This is thought to be a central component from which Parkinsonian symptoms arise.[3] This is supported by the fact that STN firing rates increase as the disease progresses and dopaminergic loss in the substantia nigra increases.[4] With more data, the classic model for Parkinsonian pathogenesis has been modified significantly. For DBS, it is not only important to understand this overall model but also to understand the different symptoms that arise from stimulation in different sites within the STN, GPi or Vim.

The classic model of Parkinsonian pathophysiology seems only to explain akinetic features of the disease. In the classic model, the substantia nigra dopaminergic loss leads to a loss of input to the putamen. This translates to clinical akinetic symptoms, but it does not always render tremors.[5] Several studies have shown that Parkinsonian tremor seems to have a distinct pathophysiology from the other cardinal symptoms of PD.[6,7] Dopaminergic therapy shows a consistent effect on the akinetic and bradykinesia symptoms in patients but is not consistent with tremors. Imaging of dopaminergic cells does not consistently correlate with PD tremor severity either.[8-10] Therefore, the classic model and the dopaminergic loss cannot fully explain tremor. Several studies suggest that both the cerebello-thalamo-cortical and spino-thalamo-cortical pathways are central to tremor.[11] Other criticisms of the firing rate theory pose issues as well. According to the model, the role of the GPi is a central component of the overall circuit, but inactivation of the GPi in animal models does not result in motor dysfunction.[12] Furthermore, pallidotomy has also been used to alleviate L-dopa-induced dyskinesias, which does not follow the expected effect of decreased GP activity.[13]

Firing pattern model

Newer models suggest that the firing patterns rather than firing rates play a role in the pathophysiology of PD. In the PD state, the central components of the basal ganglia have an abnormal synchronisation of neural firings.[14] PD medication and DBS and have been shown to disrupt this synchronisation, leading to motor improvements.[15,16] Single unit activity and local field potential analysis verify this model and show the abnormal synchronised activity.[17] In the MPTP primate model, the STN, GPi and GPe have irregular synchronised neural firings.[18] Several studies have demonstrated both a low and high frequency oscillation relating to PD tremor. In PD patients, the thalamus and basal ganglia structures have been shown to have prominent oscillatory neuron activation in the muscular activity and tremor frequency band of 4–6 Hz and the beta band frequency of 13–30 Hz, respectively, indicating the central involvement of these structures in the pathophysiology of PD.[19] The STN and GPi were seen to have greater oscillation activity in the beta band, which seems to be suppressed with dopaminergic medication and treatment. There is also a correlation between increased beta activity and UPDRS scores.[20] LFP recordings confirm the presence of a beta band in PD patients in the off-state.[20]

The exact mechanism that the beta band controls is still unclear. Beta bursts are suppressed during continuous motion, especially before and during movement.[21] The suppression of beta is diminished over time, which indicates that the worsening of the performance is correlated with increased beta oscillation. Furthermore, to cancel a prepared movement in a Go and No-Go model, the beta band activity is increased for the antikinetic movement. Further studies have found that tremors in different muscle groups or stopping motions can cause oscillatory activity in distinct frequency bands.[22-24]

Gamma activity in the 50–200 Hz range was also shown to have coupling synchrony with the beta band in PD. Dystonic patients do not express this coupling. However, this does not seem to be caused by altered neural activity and may be caused by the beta band itself.[25] With the loss of dopamine, the GPe-STN projection could cause oscillator activity by controlling the GPi-thalamus-cortex projections.[26] The synchronisation is not limited to the basal ganglia. Tremor and akinetic PD dominant patients have shown synchronisation in the putamen, which supports the firing rates theory on striatal dopamine depletion affecting the indirect pathways of neural activity.[27] There are indications that the striatum and cortical input to these structures drive oscillatory activity.

Studies have not shown any consistent homology for PD tremor, so the model of firing patterns may never encompass all patients.[28] This is especially true with the differing nature of oscillations between patients. There is a minority of PD patients who do not express the beta band or gamma band synchronisation, conflicting with the idea that this concept is central to the symptomology of the patient. Therefore, it is necessary to consider both these models as essential to understanding the basic ideas behind PD pathophysiology.

DBS EFFECTS ON THE HETEROGENEITY OF PARKINSONIAN CONDITIONS

Vim

The Vim thalamic nucleus has been an effective location for stimulation or lesioning to control PD tremor and ET. PD patients will typically be affected by resting tremors, while ET patients will be affected by postural or kinetic tremors. The Vim, along with the cerebellum and pons, is central to the tremor pathway. The cerebellum sends glutamatergic projections to the Vim.[29] Thalamic inhibition of the overactive projections within the cerebello-thalamo-cortical network through Vim DBS seems to be essential to help reduce tremors. It has been suggested that high-frequency DBS will uncouple several common neural firing pathways.[30] In ET patients with Vim DBS, regional cerebral blood flow of the cortex showed both excitatory and inhibitory effects, demonstrating the different fibre tracts that the current spreads through.[31] Vim DBS has been shown to reduce the neural activity of the motor cortex and anterior cerebellum.[32] Regarding the firing pattern alteration, alpha and theta activity in the cortex were desynchronised with Vim stimulation.[33] However, thalamotomy results in similar tremor control with very different effects on the alpha and theta waves. The firing pattern rate model still needs a lot of work to fully understand due to the variability between subjects and differing literature. PD with tremor-dominated symptoms has been shown to have a larger effect with DBS treatment in the Vim over the STN. Targeting both these structures has been shown to be very effective in reducing tremors for PD patients as well.[34] While the differing baselines of patients lead to an unclear conclusion from these results, Vim is a less optimal target for akinetic symptoms in PD. Due to this reason, it is not an effective site for other symptoms of PD compared to the STN and GPi, and it is not used often. Vim DBS is a much better option for ET patients, which is emphasised by the fact that kinaesthetic cells in the Vim are more active in ET patients than PD patients.[35] However, there is a discussion about the fact that STN stimulation does not alter the cerebellum activity to the extent that Vim stimulation does, so it is still used in tremor-dominated PD patients.[36] In an intraoperative study, the ventroposterior site of the Vim was shown to be the best site for implantation for tremors.[30] Due to substantial variability in patient-specific anatomy, ongoing research with microelectrode recordings is being utilised to improve the accuracy of implantation in the ventroposterior border.[37]

STN

The STN is the excitatory node of the basal ganglia and is central to the control of movement. The STN has been shown to help with various PD symptoms, demonstrating its importance to the pathogenesis of the disease. In animal models, it has been demonstrated that the STN in the PD state has increased firing rates and synchrony.[38-46] STN DBS clinical improvements are correlated with the reduction in the beta band synchrony.[24,46] The wide window of therapeutic options from STN DBS may be due to an antidromic effect of stimulation. Although not directly supported by some animal studies, one theory suggests that STN activity in the 4–6 Hz tremor range is perpetuated to the GPi and then the cortex.[26,43] STN stimulation can disrupt this loop and can result in spontaneous activity in the basal ganglia. The tissue activated around the STN, such as the cerebellothalamic fibres or the zona incerta, can also contribute to its effects on tremors.[44,45] However, STN stimulation seems to affect the rigidity pathway much more significantly than the tremor pathway.[36] There is a large variability of 37–89% tremor reduction rates with STN DBS, which could be due to variable lead location and patient-specific anatomy.[47] A recent study demonstrated the greatest motor benefits and levodopa reduction rates for PD were seen in patients with a posterolateral portion of the STN where the beta band activity is the greatest and, thereby, a potential high therapeutic region.[48] However, this is an area in need of further research as other studies have shown conflicting outcomes based on lead location.[48]

GPi

GPi DBS has several benefits for PD and dystonia, a neurological disorder characterised by uncontrollable muscle contractions. GPi DBS has a somatotopic organisation that affects different parts of the body at varying levels.[49] Like the STN, GPi in the DBS reduces the beta band. However, there is conflicting literature on the effect that GPi DBS has on cortical synchronisation. Both the STN and GPi DBS are effective in reducing PD tremors.[50,51] GPi DBS can affect the STN through the GPe cell projections from the GPi through the STN.

GPi DBS has been shown to improve dystonic symptoms better than STN DBS. However, in several PD GPi DBS cases, stimulation-induced dystonic (SIDs) symptoms were observed during the post-programming phase of DBS implantation. These symptoms may also be due to the lead placement. The lack of literature on these side-effects can be a product of the large overall motor improvements, leading to the SIDs going unnoticed. One such study noted dystonia following stimulation; yet, it did not record the precise location of contacts within the GPi, thus hindering the ability to ascertain the underlying causes of SIDs.[52] On the other hand, GPi stimulation has been shown to improve dystonia and heighten Parkinsonism in Huntington's Disease and craniocervical dystonia patients.[53,54] This demonstrates the known likelihood in the connection of physiology between the movement disorders.

Dystonia electrophysiological data show a decrease in the mean discharge rates of neurons in the GPi.[55,56] This could be a result of increased inhibitory pathways from the GPe

and the striatal projection to GPi.[57] On the other hand, PD motor symptoms have been correlated with increased GPi neuronal activity.[58,59] PD patients who developed dyskinesias observed both reduced GPi neuronal firings and a non-continuous burst-like discharge rate.[59] The altered synchronisation and spontaneity of the GPi neural firings will ultimately lead to distorted cortical neuron firings and changes throughout the motor cortex.

These abnormal neuronal firings from the GPi could be spread through the pallido-thalamo-cortical circuit and this pathway could explain how stimulation induces the DSIs.[59] The ventral and dorsal GPi travel to different cortical areas, which could elucidate the varying effects of stimulations. The posteroventral GPi improves rigidity and dyskinesia, while dorsal GPi improves akinesia in PD patients.[52] Stimulation in the dorsal GPi can also antagonise the L-dopa dyskinesia in PD patients. The connectivity of these structures could determine their respective motor effects and the pathophysiology of certain movement disorders during stimulation.

CONCLUSION

Small changes in lead location can result in large effects on the patient due to the activation and inhibition of certain pathways. We discussed the optimal lead locations identified in the literature for PD within the STN, GPi and Vim. In addition, while there is no singular model for the pathogenesis of PD, the models explained in this paper demonstrate the complexity of the basal ganglia circuitry.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Obeso JA, Rodríguez-Oroz MC, Rodríguez M, Lanciego JL, Artieda J, Gonzalo N, *et al*. Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci 2000;23(10 Suppl):S8-19.
2. Lanciego JL, Luquin N, Obeso JA. Functional neuroanatomy of the basal ganglia. Cold Spring Harb Perspect Med 2012;2:a009621.
3. Obeso JA, Rodríguez-Oroz MC, Benitez-Temino B, Blesa FJ, Guridi J, Marin C, *et al*. Functional organization of the basal ganglia: Therapeutic implications for Parkinson's disease. Mov Disord 2008;23 (Suppl 3):S548-59.
4. Remple MS, Bradenham CH, Kao CC, Charles PD, Neimat JS, Konrad PE. Subthalamic nucleus neuronal firing rate increases with Parkinson's disease progression. Mov Disord 2011;26:1657-62.
5. Benamer HT, Oertel WH, Patterson J, Hadley DM, Pogarell O, Höffken H, *et al*. Prospective study of presynaptic dopaminergic imaging in patients with mild Parkinsonism and tremor disorders: Part 1. Baseline and 3-month observations. Mov Disord 2003;18:977-84.
6. Zaidel A, Arkadir D, Israel Z, Bergman H. Akineto-rigid vs. tremor syndromes in Parkinsonism. Curr Opin Neurol 2009;22:387-93.
7. Helmich RC, Hallett M, Deuschl G, Toni I, Bloem BR. Cerebral causes and consequences of Parkinsonian resting tremor: A tale of two circuits? Brain 2012;135(Pt 11):3206-26.
8. Maiti P, Manna J, Dunbar GL. Current understanding of the molecular mechanisms in Parkinson's disease: Targets for potential treatments. Transl Neurodegener 2017;6:28.
9. Kazumata K, Antonini A, Dhawan V, Moeller JR, Alterman RL, Kelly P, *et al*. Preoperative indicators of clinical outcome following stereotaxic pallidotomy. Neurology 1997;49:1083-90.
10. Cummings JL, Henchcliffe C, Schaier S, Simuni T, Waxman A, Kemp P. The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration. Brain 2011;134(Pt 11):3146-66.
11. Coenen VA, Allert N, Paus S, Kronenbürger M, Urbach H, Mädler B. Modulation of the cerebello-thalamo-cortical network in thalamic deep brain stimulation for tremor: A diffusion tensor imaging study. Neurosurgery 2014;75:657-70.
12. Nambu A, Tachibana Y, Chiken S. Cause of Parkinsonian symptoms: Firing rate, firing pattern or dynamic activity changes? Basal Ganglia 2015;5:1-6.
13. Thanvi B, Lo N, Robinson T. Levodopa-induced dyskinesia in Parkinson's disease: Clinical features, pathogenesis, prevention and treatment. Postgrad Med J 2007;83:384-8.
14. Galvan A, Devergnas A, Wichmann T. Alterations in neuronal activity in basal ganglia-thalamocortical circuits in the Parkinsonian state. Front Neuroanat 2015;9:5.
15. Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: Networks, models and treatments. Trends Neurosci 2007;30:357-64.
16. Heimer G, Bar-Gad I, Goldberg JA, Bergman H. Dopamine replacement therapy reverses abnormal synchronization of pallidal neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of parkinsonism. J Neurosci

2002;22:7850-5.
17. Shimamoto SA, Ryapolova-Webb ES, Ostrem JL, Galifianakis NB, Miller KJ, Starr PA. Subthalamic nucleus neurons are synchronized to primary motor cortex local field potentials in Parkinson's disease. J Neurosci 2013;33:7220-33.
18. Wichmann T, Soares J. Neuronal firing before and after burst discharges in the monkey basal ganglia is predictably patterned in the normal state and altered in Parkinsonism. J Neurophysiol 2006;95:2120-33.
19. Du G, Zhuang P, Hallett M, Zhang YQ, Li JY, Li YJ. Properties of oscillatory neuronal activity in the basal ganglia and thalamus in patients with Parkinson's disease. Transl Neurodegener 2018;7:17.
20. Neumann WJ, Degen K, Schneider GH, Brücke C, Huebl J, Brown P, *et al*. Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. Mov Disord 2016;31:1748-51.
21. Steiner LA, Neumann WJ, Staub-Bartelt F, Herz DM, Tan H, Pogosyan A, *et al*. Subthalamic beta dynamics mirror Parkinsonian bradykinesia months after neurostimulator implantation. Mov Disord 2017;32:1183-90.
22. Brazhnik E, Novikov N, McCoy AJ, Cruz AV, Walters JR. Functional correlates of exaggerated oscillatory activity in basal ganglia output in hemiparkinsonian rats. Exp Neurol 2014;261:563-77.
23. Avila I, Parr-Brownlie LC, Brazhnik E, Castañeda E, Bergstrom DA, Walters JR. Beta frequency synchronization in basal ganglia output during rest and walk in a hemiparkinsonian rat. Exp Neurol 2010;221:307-19.
24. Oswal A, Brown P, Litvak V. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr Opin Neurol 2013;26:662-70.
25. Van Wijk BC. Is broadband gamma activity pathologically synchronized to the beta rhythm in Parkinson's disease? J Neurosci 2017;37:9347-9.
26. Wilson CL, Cash D, Galley K, Chapman H, Lacey MG, Stanford IM. Subthalamic nucleus neurones in slices from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mice show irregular, dopamine-reversible firing pattern changes, but without synchronous activity. Neuroscience 2006;143:565-72.
27. Zhang J, Wei L, Hu X, Xie B, Zhang Y, Wu GR, *et al*. Akinetic-rigid and tremor-dominant Parkinson's disease patients show different patterns of intrinsic brain activity. Parkinsonism Relat Disord 2015;21:23-30.
28. Carbon M, Argyelan M, Habeck C, Felice Ghilardi M, Fitzpatrick T, Dhawan V, *et al*. Increased sensorimotor network activity in DYT1 dystonia: A functional imaging study. Brain 2010;133(Pt 3):690-700.
29. Kuramoto E, Fujiyama F, Nakamura KC, Tanaka Y, Hioki H, Kaneko T. Complementary distribution of glutamatergic cerebellar and GABAergic basal ganglia afferents to the rat motor thalamic nuclei. Eur J Neurosci 2011;33:95-109.
30. Milosevic L, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD. Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression [published correction appears in Brain 2018;141:e72]. Brain 2018;141:2142-55.
31. Haslinger B, Boecker H, Büchel C, Vesper J, Tronnier VM, Pfister R, *et al*. Differential modulation of subcortical target and cortex during deep brain stimulation. Neuroimage 2003;18:517-24.
32. Baron JC, Levasseur M, Mazoyer B, Legault-Demare F, Mauguière F, Pappata S, *et al*. Thalamocortical diaschisis: Positron emission tomography in humans. J Neurol Neurosurg Psychiatry 1992;55:935-42.
33. Air EL, Ryapolova-Webb E, de Hemptinne C, Ostrem JL, Galifianakis NB, Larson PS, *et al*. Acute effects of thalamic deep brain stimulation and thalamotomy on sensorimotor cortex local field potentials in essential tremor. Clin Neurophysiol 2012;123:2232-8.
34. Fayed I, Cobourn KD, Pivazyan G, Torres-Yaghi YA, Pagan FL, Lo SE, *et al*. Combination targeting of subthalamic nucleus and ventral intermediate thalamic nucleus with a single trajectory in deep brain stimulation for tremor-dominant Parkinson's disease. J Clin Neurosci 2021;85:92-100.
35. Molnar GF, Pilliar A, Lozano AM, Dostrovsky JO. Differences in neuronal firing rates in pallidal and cerebellar receiving areas of thalamus in patients with Parkinson's disease, essential tremor, and pain. J Neurophysiol 2005;93:3094-101.
36. Mure H, Hirano S, Tang CC, Isaias IU, Antonini A, Ma Y, *et al*. Parkinson's disease tremor-related metabolic network: Characterization, progression, and treatment effects. Neuroimage 2011;54:1244-53.
37. King NK, Krishna V, Sammartino F, Bari A, Reddy GD, Hodaie M, *et al*. Anatomic targeting of the optimal location for thalamic deep brain stimulation in patients with essential tremor. World Neurosurg 2017;107:168-74.
38. Hassani OK, Féger J. Effects of intrasubthalamic injection of dopamine receptor agonists on subthalamic neurons in normal and 6-hydroxydopamine-lesioned rats: An electrophysiological and c-Fos study. Neuroscience 1999;92:533-43.
39. Kreiss DS, Mastropietro CW, Rawji SS, Walters JR. The response of subthalamic nucleus neurons to dopamine receptor stimulation in a rodent model of Parkinson's disease. J Neurosci 1997;17:6807-19.
40. Liu X, Ford-Dunn HL, Hayward GN, Nandi D, Miall RC, Aziz TZ, *et al*. The oscillatory activity in the Parkinsonian subthalamic nucleus investigated using the macro-electrodes for deep brain stimulation. Clin Neurophysiol 2002;113:1667-72.
41. Nambu A. A new dynamic model of the cortico-basal ganglia loop. Prog Brain Res 2004;143:461-6.
42. Mandali A, Chakravarthy VS, Moustafa AA. A neuro-computational model of pallidal vs. subthalamic deep brain stimulation effect on synchronization at tremor frequency in Parkinson's disease. In: Multiscale models of brain disorders. Vol. 13. Cham: Springer; 2019.
43. Bevan MD, Atherton JF, Baufreton J. Cellular principles underlying normal and pathological activity in the subthalamic nucleus. Curr Opin Neurobiol 2006;16:621-8.
44. Montgomery EB Jr., Gale JT. Mechanisms of action of deep brain stimulation (DBS). Neurosci Biobehav Rev 2008;32: 388-407.
45. Kühn AA, Kempf F, Brücke C, Doyle LG, Martinez-Torres I, Pogosyan A, *et al*. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement

in motor performance. J Neurosci 2008;28:6165-73.
46. Oswal A, Beudel M, Zrinzo L, Limousin P, Hariz M, Foltynie T, *et al*. Deep brain stimulation modulates synchrony within spatially and spectrally distinct resting state networks in Parkinson's disease. Brain 2016;139(Pt 5):1482-96.
47. Iorio-Morin C, Fomenko A, Kalia SK. Deep-brain stimulation for essential tremor and other tremor syndromes: A narrative review of current targets and clinical outcomes. Brain Sci 2020;10:925.
48. Vitek JL, Patriat R, Ingham L, Reich MM, Volkmann J, Harel N. Lead location as a determinant of motor benefit in subthalamic nucleus deep brain stimulation for Parkinson's disease. Front Neurosci 2022;16:1010253.
49. Baker KB, Lee JY, Mavinkurve G, Russo GS, Walter B, DeLong MR, *et al*. Somatotopic organization in the internal segment of the globus pallidus in Parkinson's disease. Exp Neurol 2010;222:219-25.
50. Wong JK, Cauraugh JH, Ho KW, Broderick M, Ramirez-Zamora A, Almeida L, *et al*. STN vs. GPi deep brain stimulation for tremor suppression in Parkinson disease: A systematic review and meta-analysis. Parkinsonism Relat Disord 2019;58:56-62.
51. Nozile-Firth K, Viswanathan V, Zamora AR, Foote K, Okun M, Wagle-Shukla A. Comparison of STN and GPi DBS in patients with Parkinson's disease and substantial Action/Postural Tremor. Neurology 2018;90:(15_supplement).
52. Yelnik J, Damier P, Bejjani BP, Francois C, Gervais D, Dormont D, *et al*. Functional mapping of the human globus pallidus: Contrasting effect of stimulation in the internal and external pallidum in Parkinson's disease. Neuroscience 2000;101:77-87.
53. Moro E, Lang AE, Strafella AP, Poon YY, Arango PM, Dagher A, *et al*. Bilateral globus pallidus stimulation for Huntington's disease. Ann Neurol 2004;56:290-4.
54. Zauber SE, Watson N, Comella CL, Bakay RA, Metman LV. Stimulation-induced parkinsonism after posteroventral deep brain stimulation of the globus pallidus internus for craniocervical dystonia. J Neurosurg 2009;110:229-33.
55. Lozano AM, Kumar R, Gross RE, Giladi N, Hutchison WD, Dostrovsky JO, *et al*. Globus pallidus internus pallidotomy for generalized dystonia. Mov Disord 1997;12:865-70.
56. Vitek JL, Zhang J, Evatt M, Mewes K, DeLong MR, Hashimoto T, *et al*. GPi pallidotomy for dystonia: Clinical outcome and neuronal activity. Adv Neurol 1998;78:211-9.
57. DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990;13:281-5.
58. Boraud T, Bezard E, Bioulac B, Gross C. High frequency stimulation of the internal Globus Pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. Neurosci Lett 1996;215:17-20.
59. Merello M, Balej J, Delfino M, Cammarota A, Betti O, Leiguarda R. Apomorphine induces changes in GPi spontaneous outflow in patients with Parkinson's disease. Mov Disord 1999;14:45-9.

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