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Deep brain stimulation: How does it work?

■ **ABSTRACT**

Deep brain stimulation has significantly improved the motor symptoms in patients with Parkinson's disease (PD) and other movement disorders. The mechanisms responsible for these improvements continue to be explored. Inhibition at the site of stimulation has been the prevailing explanation for the symptom improvement observed with deep brain stimulation. Research using microelectrode recording during deep brain stimulation in the MPTP monkey model of PD has helped clarify how electrical stimulation of structures within the basal ganglia–thalamocortical circuit improves motor symptoms, and suggests that activation of output and the resultant change in pattern of neuronal activity that permeates throughout the basal ganglia motor circuit is the mechanism responsible for symptom improvement.

Whether deep brain stimulation can dramatically help patients with Parkinson's disease (PD) and other movement disorders is no longer questioned. Rather, *how* it works is not well understood: how do patients with seemingly diverse conditions show improvement with the same intervention?

Patients with advanced PD often freeze when trying to walk and have tremor, rigidity, bradykinesia, and gait and balance problems. With deep brain stimulation, a patient typically experiences a marked improvement in these motor symptoms.

Similarly, patients with hypokinetic disorders such as generalized dystonia who have extensive involuntary movements involving multiple body parts may experience a significant reduction in these movements and regain function during deep brain stimulation. In my experience, it is not unusual for patients who were not ambulatory as a result of their dystonic movements to regain function to the point where they can walk unassisted and, in some cases, participate in physical activities such as racquetball or jogging on a treadmill. One of my patients with generalized dystonia could walk no farther than several meters before deep brain stimulation but afterward was able to run on a treadmill. This patient did not gain this type of function immediately after stimulation, but after sustained efforts at programming his stimulation device over the course of 1 year he was able to travel to Europe, hike in the mountains, and jog on a treadmill.
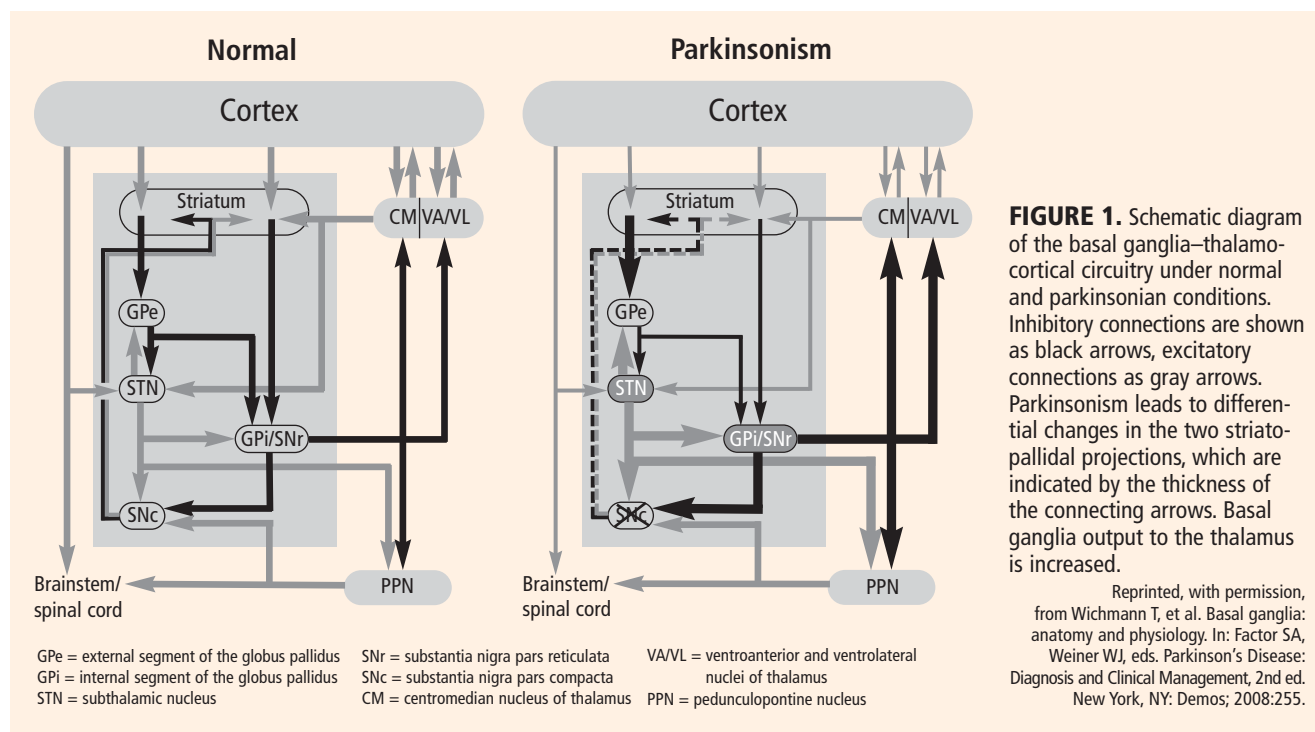
In addition to treating movement disorders, deep brain stimulation is being used experimentally to treat patients with behavioral disorders such as depression and obsessive-compulsive disorder that are refractive to standard therapy. Broadening our understanding of the mechanisms responsible for success with deep brain stimulation is important since it may help to improve current applications and develop new ones. This article discusses our research in deep brain stimulation using microelectrode recording of structures within the basal ganglia–thalamocortical circuit in the MPTP monkey model of PD.

■ **INSIGHTS INTO MECHANISMS OF STIMULATION PROMISE TECHNOLOGICAL REFINEMENTS**

One rationale for attempting to better understand how deep brain stimulation works is that such knowledge may enable us to improve the technology to better apply the technique.

Electrode design is one important area of potential improvement. Diseases that may one day be treated with deep brain stimulation will likely require electrodes of different shapes than those used currently, to accommodate other targets in the brain. At present, a single lead shape is used to stimulate the subthalamic nucleus (STN) and the globus pallidus internus (GPi) for treating PD. Possible future targets include the globus pallidus externus (GPe), various subnuclei of the thalamus, portions of the striatum, and other subcortical and cortical structures that have different geometric configurations and physiologic characteristics. Since these structures and regions of the brain differ from one another in size and shape, it is highly likely that new electrode designs will be needed to take advantage of

Normal   **Parkinsonism**

FIGURE 1. Schematic diagram of the basal ganglia–thalamocortical circuitry under normal and parkinsonian conditions. Inhibitory connections are shown as black arrows, excitatory connections as gray arrows. Parkinsonism leads to differential changes in the two striato-pallidal projections, which are indicated by the thickness of the connecting arrows. Basal ganglia output to the thalamus is increased.

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GPe = external segment of the globus pallidus
GPi = internal segment of the globus pallidus
STN = subthalamic nucleus
SNr = substantia nigra pars reticulata
SNc = substantia nigra pars compacta
CM = centromedian nucleus of thalamus
VA/VL = ventroanterior and ventrolateral nuclei of thalamus
PPN = pedunculopontine nucleus

this geometric and physiologic variability. Future electrodes may vary in size and shape from those used currently, incorporate three-dimensional designs, and require a current source that allows the pattern of stimulation to be varied based on the physiologic changes that characterize each neurologic disorder.

Directionality may be another important feature of electrode design. With presently used electrodes, electric current spreads in all directions. To spread the current or increase the volume of tissue affected by stimulation, one must increase the voltage being passed through the lead. This results in a larger region of tissue being affected by stimulation, but the current density varies based on distance from the stimulation site, with neural tissue close to the site being affected differently from tissue that is farther away. Moreover, the current cannot be directed or aimed in one direction or the other. A split-band design could spread current in opposing directions, and a three-dimensional directional design involving several contacts could affect a volume of tissue more homogeneously.

■ **PROGRESS IN DEFINING PD PATHOPHYSIOLOGY**

As with any disease, defining the problem and understanding the underlying pathophysiology are essential first steps to finding an effective treatment for PD. In the 1930s and 1940s, numerous attempts were made to treat PD with surgical therapies. Surgical targets were chosen throughout the length of the neuraxis, includ-

ing the cortex, the internal capsule, the basal ganglia, the thalamus, the cerebral peduncle, and the spinal cord itself. The underlying pathophysiology was not well understood, however, so the rationale for surgery was weak at best. For example, lesioning the cortex improved parkinsonian tremor, but it also caused paralysis and was associated with considerable morbidity.

Evidence of a common circuit

Over time, a number of anatomic and physiologic studies provided evidence that there may be a common anatomy or circuit that malfunctions between the diverse disorders that are now improved with deep brain stimulation. It is now recognized that PD and dystonia—disorders that involve a paucity of movement and excessive movement, respectively—both result from disorders of the basal ganglia. Similarly, the basal ganglia–thalamocortical circuit appears to play an integral role in behavioral disorders such as depression, schizophrenia, autism, and obsessive-compulsive disorder. This basal ganglia–thalamocortical circuit includes connections from the cortex, through the basal ganglia, and back to the cortex through the thalamus **(Figure 1)**. Different regions within nodal points (striatum, GPe, GPi, STN, thalamus) of the circuit affect movement, cognition, and behavior, so that malfunction in different regions of each nodal point in the circuit may result in different neurologic disorders.

In PD, degeneration of dopamine-producing neurons

in the substantia nigra pars compacta reduces dopamine levels in the striatum. In MPTP monkey models of PD there is also a loss of dopamine-producing cells in the substantia nigra pars compacta. These animals develop the cardinal motor symptoms of PD and are considered a good model of the human disorder. By recording from the basal ganglia–thalamocortical circuit in this model, we and others have observed excessive activity in the STN and GPi.[1-4] In addition, cells in these regions in the monkey model were more likely to discharge in bursts compared with cells from healthy monkeys, and they showed a higher degree of synchronized oscillatory activity among neighboring neurons.[5,6]

Ultimate goal: The ability to individualize therapy

Understanding how such changes relate to parkinsonian symptoms will enable us to develop stimulation strategies that are focused on ameliorating the particular physiologic changes in PD. Since PD can lead to distinctly different clinical pictures, it would be ideal to be able to individualize therapy based on the particular motor symptoms each patient experiences. This may require stimulation strategies that affect either a particular region of the targeted structure or a particular physiologic change that occurs in the disease state.

■ THE 'RATE HYPOTHESIS': ALTERED CELLULAR DISCHARGE RATES CAUSE PARKINSONIAN MOTOR SYMPTOMS

A good model for PD was lacking prior to the 1980s. As a result, there was little understanding of the pathophysiologic basis for this disorder. A breakthrough in the mid-1980s revolutionized research in this field. A group of young people developed parkinsonian symptoms, and it was discovered that they had all used recreational "designer drugs" containing an impurity: the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Now given to primates to simulate PD, MPTP causes all of the classic symptoms of PD except tremor (this may vary from species to species), including freezing, slowness, stiffness, and gait and balance problems. Like humans with PD, primates with MPTP-induced PD even develop dyskinesia after prolonged treatment with levodopa.

Experimentation with MPTP monkeys in the late 1980s led to the "rate hypothesis," which basically states that when dopamine production is reduced from the substantia nigra compacta (as in PD), changes in striatal activity lead to suppression of GPe activity and a reduction in inhibitory output from the GPe to the STN. This decrease in inhibitory output allows the STN to be overactive, which, in conjunc-

tion with a reduction of direct striatal inhibition of the GPi, causes excessive GPi activity and a suppression of thalamic activity to the cortex **(Figure 1)**.

When recording electrodes were placed in these structures in the monkey brain, rate changes were reported to occur in each of these structures in the parkinsonian state.[1-4,7] Action potentials recorded from the GPi in MPTP-treated monkeys occurred at a much faster rate than those in healthy monkeys.

Pallidotomy revisited: Dramatic symptom improvement is possible

On the basis of the above and other studies in the MPTP monkey model of PD, investigators in the 1990s reasoned that reduced dopamine in PD led to excessive activity in portions of this circuit. While I would like to say that this led to the rationale for lesioning the STN and GPi for the treatment of PD, this approach had already been taken in the early 1930s and 1940s and continued into the 1960s; it was largely stopped with the introduction of levodopa and was restarted again after the realization that chronic levodopa therapy was associated with a variety of side effects, including the development of excessive involuntary movement and motor fluctuations.

Pallidotomy (lesioning of the pallidum), although tried as a treatment for PD in the 1930s and 1940s, had been abandoned as a result of its inconsistent benefit and lack of effect on parkinsonian tremor. It underwent a resurgence in the 1990s through the work of a group in New York[8] that revived Lars Leksell's pallidotomy approach of the 1960s[9] at a time when basic science studies provided the rationale for surgical therapy to create lesions in the GPi. These basic science studies also provided critical new information about the optimal site for lesioning, which led to improved and more consistent outcomes.[10-13] In the early years, lesions were created in the anterior (nonmotor) portion of the pallidum but led to inconsistent results. In the 1990s, with a better understanding of the portion of the pallidum involved in motor control, destroying brain tissue by creating a lesion in the posterolateral "motor" region of the pallidum resulted in such dramatic improvement in motor signs that waiting lists of up to 4 years were common for patients who wanted the procedure.

Although unilateral pallidotomy led to marked improvement in motor symptoms on the contralateral side, attempts at bilateral lesions to improve both sides of the body, as well as axial symptoms, were associated with marked hypophonia and, in some reports, cognitive decline. This led physicians and scientists to search for a procedure that could be performed
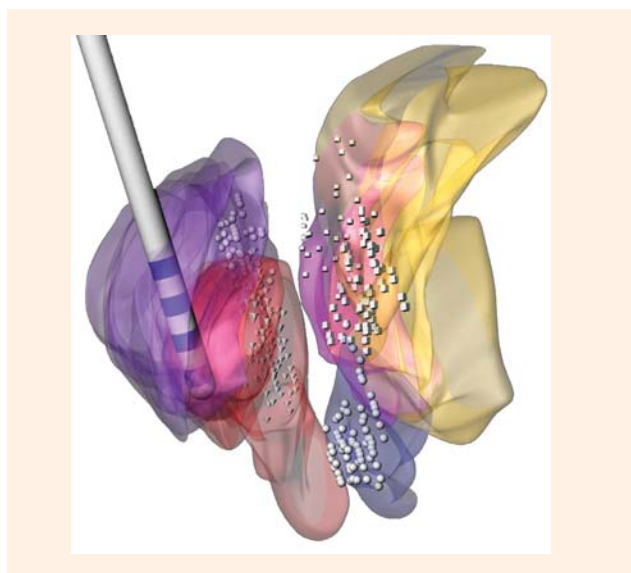
FIGURE 2. Image generated by software designed to assist in lead placement in a monkey model of Parkinson's disease.[16] The various subcortical structures are represented in different colors. In this example, the thalamus is yellow, the subthalamic nucleus is gray, the globus pallidus externus (GPe) is purple, and the globus pallidus internus (GPi) is red/pink. The lead is passing through the GPe and GPi with the contacts denoted by the purple bands. Each cell from which recordings are made is denoted by a white symbol.

bilaterally without the high incidence of side effects associated with lesioning procedures—and thus to the birth of deep brain stimulation.

Deep brain stimulation as lesion simulation

During the early experience with pallidotomy, the area to be lesioned would first be stimulated with the lesioning probe to observe its effects and thereby determine the precise area in which to create a lesion. At the time, no mechanism existed to leave the stimulator in place rather than create a lesion. But after the development of implantable stimulation devices, chronic stimulation could be delivered bilaterally to the pallidum and STN, resulting in a markedly improved treatment. Since side effects associated with stimulation are reversible, the ability to perform such procedures on both sides of the brain and to adjust stimulation parameters in order to optimize benefits while minimizing side effects made deep brain stimulation the procedure of choice for patients with advanced PD and led to its exploration for treatment of other neurologic disorders.

Because stimulation produced the same or similar benefit as a lesion, most physicians thought that stimulation must work in a similar manner, ie, by decreasing output from the stimulated structure. The rationale for this hypothesis received support from the "rate" model of PD, which postulated that PD motor symptoms

occur as a result of overactivity in the STN and GPi. It was postulated that deep brain stimulation improved clinical symptoms by suppressing output from the stimulated structure—in other words, deep brain stimulation effectively caused a physiologic ablation.[14,15]

■ FURTHER RESEARCH GIVES RISE TO THE 'PATTERN HYPOTHESIS'

Deep brain stimulation in the monkey model

To test the effects of deep brain stimulation, we have performed it in primates with MPTP-induced parkinsonism. Custom-made leads sized to fit a monkey brain are implanted in the same deep brain structures that are targeted when treating PD in humans. Each animal lead has four contacts 0.5 mm in size. We implant a pulse generator, connect the pulse generator to the lead, and set stimulation parameters to improve motor symptoms to mimic a human therapeutic setting as closely as possible. We then record from the basal ganglia structures before, during, and after stimulation that improves the monkey's motor symptoms. This allows us to determine which changes in neuronal activity in the basal ganglia circuit during stimulation are associated with an improvement in motor symptoms.

Chamber placement and orientation as well as lead placement are determined with the help of a software program and information from magnetic resonance imaging and computed tomography, similar to the process for neurosurgery in humans.[16] The software also allows for mapping the location of every cell from which recordings are taken (**Figure 2**).

In earlier studies examining the mechanism underlying deep brain stimulation, neural activity was recorded only after stimulation, so that activity that occurred during stimulation had to be inferred from that which occurred immediately after stimulation was stopped. We developed a method to subtract artifact produced from stimulation without losing data. This method has been validated, is now used in a number of laboratories, and has revolutionized our ability to study the effect of stimulation on neuronal activity.[17]

A paradoxical finding

Based on the rate hypothesis, we expected that increased output from the GPi would cause parkinsonian symptoms and predicted that stimulation of the STN should suppress its output, which would suppress excitatory activity to the GPi from the STN and thereby reduce its output. Reduction of the inhibitory output from the GPi to the thalamus would, in turn, lead to a restoration of thalamocortical function and a reduction in the motor signs associated with PD. However, stimulating the STN was found to *increase* GPi activity.[18]
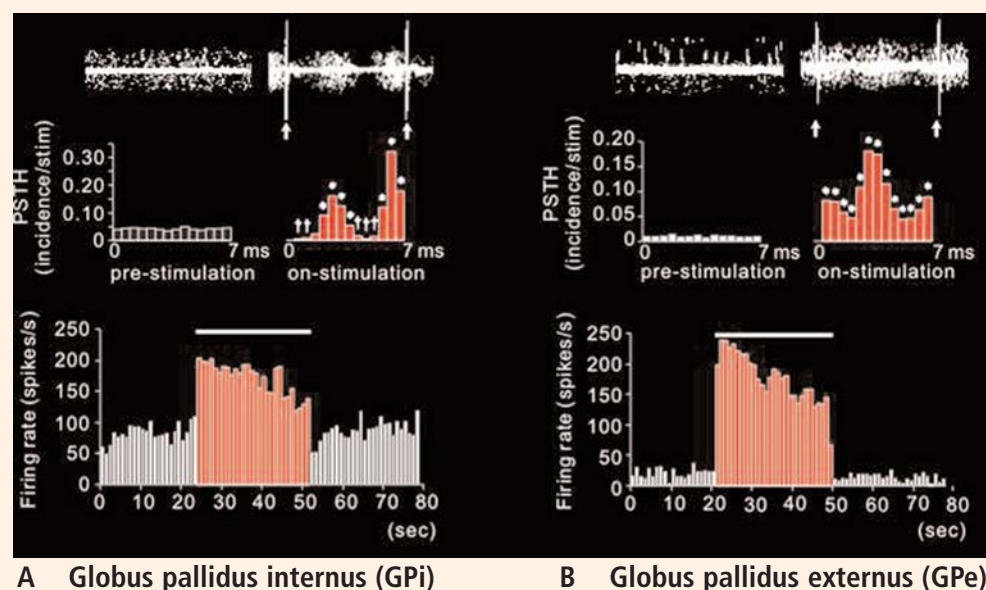
FIGURE 3. Examples of neuronal responses occurring during subthalamic nucleus stimulation in (A) a GPi cell and (B) a GPe cell.
Top: Analog signal overlays of 100 sweeps made by triggering at 10-ms intervals in the prestimulation period (before start of stimulation) and by triggering on the stimulation pulse in the on-stimulation period. Arrows indicate residual stimulation artifacts after artifact template subtraction.
Middle: Peristimulus time histograms (PSTHs) reconstructed from successive 7.0-ms time periods in the prestimulation period and from the inter-stimulus periods (7.3 ms) in the on-stimulation period. The first PSTH bin is omitted in the on-stimulation period because of signal saturation and residual stimulation artifacts. Asterisks denote a significant increase at $P < .01$, and daggers denote a significant decrease at $P < .01$ (Wilcoxon signed rank test). **Bottom:** Mean firing rate calculated every 1 sec on the basis of the PSTH, illustrating the time course of the firing rate.

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Despite increased rates, the incidence and intensity of symptoms were reduced. Further complicating the picture, we were contemporaneously exploring the effect of creating lesions in other parts of the basal ganglia that also led to increased rates of GPi activity, but in this case we observed that the increased rates were associated with a worsening of motor symptoms. In short, we had two laboratories working in parallel that had apparently obtained opposite results: increased GPi activity was associated with improved symptoms in one laboratory and with worse symptoms in the other.[18,19]

Patterns of activity are more important than rate
This seeming paradox may be explained by evaluating the data with a post-stimulus time histogram **(Figure 3)**. Simple recordings of activity show seemingly random action potentials over time; however, if activity is recorded repeatedly during stimulation and the overall data are averaged, action potentials are observed to occur in a definite pattern, with action potentials in GPi neurons occurring mainly at 3 ms and 6 ms after a stimulation pulse in the STN. The number of cells showing a particular pattern of response could be changed by varying the stimulation parameters. This shift in the population of neurons that showed such a stereotyped pattern of response under stimulation parameters that improved motor symptoms may offer part of the explanation for our apparent paradox: stimulation that improved motor symptoms regularized that spike train, while the lesions we produced in the GPe that increased the rate did not change the irregularity in the spike train. These observations provided compelling data to support the hypothesis that motor symptoms associated with PD, and possibly other movement and nonmovement disorders, may occur as a result of changes in the pattern of neuronal activity rather than changes in rate.

Knowledge that stimulation activated output from the stimulated region and changed the pattern of neuronal activity led us to ponder whether other targets, or even other ways to deliver stimulation, might work better to improve parkinsonian symptoms.

A focus on GPe stimulation
As a result of these observations, we reasoned that since GPe activity is also altered in PD and its rates are reduced, driving the output from this region that is inhibitory to the STN and GPi may help to reduce and regularize that activity at a point in the circuit that could provide even greater improvement in the motor symptoms associated with PD. Based on this hypothe-

sis, we performed direct stimulation of the GPe in the MPTP monkey model of PD and evaluated its effect on motor behavior and neuronal activity in the circuit.

As an interesting sidelight, it should be noted that long before we developed this hypothesis, we had observations from a 1994 experiment (only recently published[20]) in which bradykinesia was improved upon acute stimulation in the GPe prior to making a lesion in the GPi. With sustained stimulation in this patient, we observed development of dyskinetic movements. Since we reasoned that lesions in this region would worsen parkinsonian symptoms—a rationale recently supported by a publication from our laboratory in 2006[19]—and since we had no means by which to stimulate this region chronically at the time, this observation was filed away and we continued with lesioning the GPi for the treatment of these patients.

However, with the advent of chronic deep brain stimulation, we opted to reexplore this series of experiments in MPTP-treated monkeys. A lead was placed such that three of its contacts were in the GPe and one was in the GPi. Bradykinesia was assessed by determining the time it took for the monkey to retrieve raisins from a Klüver board. By inducing symptoms on one side only, we were able to use the healthy side as a control. We observed that before stimulation, retrieval took more than twice as long on the affected side. Stimulation of only 2 V had no effect, but increasing the voltage to 5.5 V significantly improved retrieval time.[21]

Plotting the data using post-stimulus time histograms showed that stimulation of the GPe inhibited the STN, confirming our hypothesis that stimulation activated the output from the stimulated structure (the GPe sends inhibitory projections to the STN). The responses observed were dramatic, with the majority of cells in the STN showing almost complete suppression of activity (Vitek et al, unpublished data).

In light of this observation, we expected that the rate of activity in the GPi would be reduced. Interestingly, although the rate was changed in most cells compared with control, what was most striking was the relatively stereotyped pattern of inhibition and excitation that occurred following each pulse of GPe stimulation. Although shifted in absolute frequency, the pattern that occurred was similar to that observed during STN stimulation, with alternating periods of excitation and inhibition evident in the post-stimulus time histogram.

Further evaluation of the data revealed a change in burst and oscillatory activity in the STN. Analysis of the data showed a shift in the distribution of power from low to high frequencies. Stimulation reduced activity in the low-frequency range and increased power in higher frequencies, similar to that in normal movement.

Further analysis of the spike trains revealed that entropy (a reflection of noise in the spike signal) was reduced under stimulation parameters that resulted in a reduction in symptoms. In contrast, stimulation parameters that resulted in worsening symptoms increased measures of entropy (Dorval, data submitted for publication).

■ PATTERN CHANGES AFFECT INFORMATION PROCESSING ACROSS THE BASAL GANGLIA–THALAMOCORTICAL NETWORK

There is a lack of consensus about the precise physiologic effect of deep brain stimulation for improving symptoms in movement disorders. Many researchers continue to believe that deep brain stimulation works through inhibition. An alternate explanation is that at effective stimulation parameters, the net effect is activation of output from the stimulated structure. Various modalities, including modeling,[22,23] microdialysis,[24] functional magnetic resonance imaging,[25] and positron emission tomography,[26,27] provide additional evidence that activation occurs during stimulation.

While one cannot discount a role for rate changes in mediating the effects of deep brain stimulation, there is now increasing evidence suggesting that pattern changes induced in the network as a result of stimulation-induced activation of output from the stimulated structure play an integral role in this process.

Research often leads to unpredictable outcomes. The prevailing hypothesis a decade ago concerning the pathophysiologic basis of PD (and still believed in many centers) was that rate is the controlling factor. But we have seen in our animal models that symptoms improve with increased rate in the GPi during stimulation in the STN. Similarly, GPi rates are abnormally low in patients with dystonia and in PD patients during dyskinesia, yet lesioning in the GPi that further reduces its output leads to improvement in these conditions. Based on these observations, it would appear that rate is unlikely to be the critical factor; we now must take into account other factors, such as pattern, oscillation, and synchronization, as well as changes in the network dynamics. Deep brain stimulation is changing the informational content of the neural network, and these changes are occurring across populations of neurons through the whole basal ganglia circuit. Knowing how these changes result in improvement in the neurologic disorder being treated will be critical to our understanding of not only how deep brain stimulation works, but how to make it work better and how to apply it effectively to other neurologic disorders.

FUTURE DIRECTIONS

Future research should focus on multiunit recording simultaneously across nodal points in the basal ganglia–thalamocortical circuit to assess population and network dynamics. This approach would provide information on the real-time effects of stimulation in the network. Until now, most studies have collected recordings from one cell at a time. This is a very labor-intensive process and limits our ability to relate what happens at one point in the circuit to what happens at another point. Multiunit recording across multiple nodes within the basal ganglia–thalamocortical circuit will help us address this question and tell us what happens across populations of neurons at multiple sites in the motor circuit and how this is changed during stimulation. Such an approach will help us to better understand the pathophysiologic basis for the development of neurologic disorders and how stimulation works to improve these disorders. This information is a critical step toward the ability to knowingly change network activity in a way that is predictable and more compatible with the normal state, as well as toward the application of this technology to other disorders.

The potential for clinical applications of deep brain stimulation is dramatic, but we must proceed with caution. Indications should be based on sound scientific rationale, and outcomes must be accurately and systematically documented. Move forward we must, but with caution—most certainly.

Acknowledgments

REFERENCES

1. **DeLong MR.** Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990; 13:281–285.
2. **Filion M, Tremblay L.** Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 1991; 547:142–151.
3. **Miller WC, DeLong MR.** Altered tonic activity of neurons in the globus pallidus and subthalamic nucleus in the primate MPTP model of parkinsonism. In: Carpenter MB, Jayaraman A, eds. The Basal Ganglia II. Structure and Function: Current Concepts. New York, NY: Plenum; 1987:415–427.
4. **Bergman H, Wichmann T, Karmon B, DeLong MR.** The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. J Neurophysiol 1994; 72:507–520.
5. **Nini A, Feingold A, Slovin H, Bergman H.** Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. J Neurophysiol 1995; 74:1800–1805.
6. **Raz A, Vaadia E, Bergman H.** Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. J Neurosci 2000; 20:8559–8571.
7. **Elder C, Vitek J.** The motor thalamus: alteration of neuronal activity in the parkinsonian state. In: Kultas-Ilinsky K, Ilinsky IA, eds. Basal Ganglia and Thalamus in Health and Movement Disorders. New York, NY: Kluwer Academic Plenum Publishers; 2001:257–265.
8. **Fazzini E, Dogali M, Sterio D, Eidelberg D, Beric A.** Stereotactic pallidotomy for Parkinson's disease: a long-term follow-up of unilateral pallidotomy. Neurology 1997; 48:1273–1277.
9. **Svennilson E, Torvik A, Lowe R, Leksell L.** Treatment of parkinsonism by stereotactic thermolesions in the pallidal region. A clinical evaluation of 81 cases. Acta Psychiatr Scand 1960; 35:358–377.
10. **Vitek JL, Bakay RA, Freeman A, et al.** Randomized trial of pallidotomy versus medical therapy for Parkinson's disease. Ann Neurol 2003; 53:558–569.
11. **Dogali M, Fazzini E, Kolodny E, et al.** Stereotactic ventral pallidotomy for Parkinson's disease. Neurology 1995; 45:753–761.
12. **Lozano AM, Lang AF, Galvez-Jimenez N, et al.** Effect of GPi pallidotomy on motor function in Parkinson's disease. Lancet 1995; 346:1383–1387.
13. **Baron MS, Vitek JL, Bakay RA, et al.** Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. Ann Neurol 1996; 40:355–366.
14. **Benazzouz A, Hallett M.** Mechanism of action of deep brain stimulation. Neurology 2000; 55(12 Suppl 6):S13–S16.
15. **Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM.** Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol 2000; 84:570–574.
16. **Miocinovic S, Zhang J, Xu W, et al.** Stereotactic neurosurgical planning, recording, and visualization for deep brain stimulation in nonhuman primates. J Neurosci Methods 2007; 162:32–41.
17. **Hashimoto T, Elder CM, Vitek JL.** A template subtraction method for stimulus artifact removal in high-frequency deep brain stimulation. J Neurosci Methods 2002; 113:181–186.
18. **Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL.** Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosci 2003; 23:1916–1923.
19. **Zhang J, Russo GS, Mewes K, Rye DB, Vitek JL.** Lesions in monkey globus pallidus externus exacerbate parkinsonian symptoms. Exp Neurol 2006; 199:446–453.
20. **Vitek JL, Hashimoto T, Peoples J, DeLong MR, Bakay RA.** Acute stimulation in the external segment of the globus pallidus improves parkinsonian motor signs. Mov Disord 2004; 19:907–915.
21. **Zhang J, Russo GS, Chen X, Hashimoto T, Elder CM, Vitek JL.** Deep brain stimulation of monkey globus pallidus externus in experimental parkinsonism. Abstract presented at: 33rd Annual Meeting of the Society for Neuroscience; November 8–12, 2003; New Orleans, LA.
22. **McIntyre CC, Grill WM.** Extracellular stimulation of central neurons: influence of stimulus waveform and frequency on neuronal output. J Neurophysiol 2002; 88:1592–1604.
23. **McIntyre CC, Grill WM, Sherman DL, Thakor NV.** Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. J Neurophysiol 2004; 91:1457–1469.
24. **Windels F, Bruet N, Poupard A, et al.** Influence of the frequency parameter on extracellular glutamate and gamma-aminobutyric acid in substantia nigra and globus pallidus during electrical stimulation of subthalamic nucleus in rats. J Neurosci Res 2003; 72:259–267.
25. **Jech R, Urgosik D, Tintera J, et al.** Functional magnetic resonance imaging during deep brain stimulation: a pilot study in four patients with Parkinson's disease. Mov Disord 2001; 16:1126–1132.
26. **Perlmutter JS, Mink JW, Bastian AJ, et al.** Blood flow responses to deep brain stimulation of thalamus. Neurology 2002; 58:1388–1394.
27. **Hershey T, Revilla FJ, Wernle AR, et al.** Cortical and subcortical blood flow effects of subthalamic nucleus stimulation in PD. Neurology 2003; 61:816–821.

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