NEUROSTIMULATION
Principles and Practice
Edited by Sam Eliamel and Konstantin V. Slavin

WILEY Blackwell
We dedicate this book to:

All healthcare professionals who decided to be involved in the care of patients who underwent neurostimulation.

Our teachers and mentors in functional neurosurgery, who enabled, empowered, and taught us the skills to implant neurostimulators and to take care of patients with neurostimulators.

Our students and fellows who made the jump onto functional neurosurgery to continue the art of functional neurosurgery in years to come.

All our patients for entrusting us to help them over the years via neurostimulation.

Our families for their support over the years, providing us with the best start in life, and education, and for their support during this project.

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## Contents

List of Contributors viii  
Preface xi  

**Part 1 Deep Brain Stimulation** 1  

1 Deep Brain Stimulation: Mechanisms of Action 3  
*Erwin B. Montgomery Jr.*  

2 Overview of Deep Brain Stimulation Components 20  
*Sam Eljamel*  

3 Deep Brain Stimulation in Parkinson’s Disease: Subthalamic Nucleus 26  
*Manish Ranjan and Christopher R. Honey*  

4 Deep Brain Stimulation in Parkinson’s Disease: Pallidal (globus pallidus pars interna) 37  
*Yasuaki Harasaki and Steven Ojemann*  

5 Deep Brain Stimulation of the Pedunculopontine Nucleus for Parkinson’s Disease 44  
*Aviva Abosch and Amit Goyal*  

6 Deep Brain Stimulation in Tremor 54  
*Antonios Mammis and Michael Schulder*  

7 Deep Brain Stimulation in Dystonia 63  
*Ludvic Zrinzo*  

8 Deep Brain Stimulation in Epilepsy 72  
*Michael G. Kaplitt*  

9 Deep Brain Stimulation in Obsessive Compulsive Disorders 82  
*David Christmas and Loes Gabriëls*  

10 Deep Brain Stimulation in Treatment of Refractory Major Depression 89  
*Clement Hamani and Paul E. Holtzheimer*  

11 Deep Brain Stimulation in Pain Syndromes 97  
*Alexander Green*  

12 Deep Brain Stimulation in Cluster Headache 104  
*Giovanni Broggi, Giuseppe Messina, and Angelo Franzini*
Appendix I: Principles of Programming of Neurostimulators  
Sam Eljamel, Patrick Carena, and Catherine Young  
219

Appendix II: Troubleshooting Malfunctioning Neurostimulators  
Sam Eljamel  
222

Index  
231

Colour plate section to appear between pages 84 and 85
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Preface

*Neurostimulation: Principles and Practice* is intended to give a concise but comprehensive picture of the methods and devices which are now of use in neurostimulation to ameliorate the symptoms of Parkinson’s disease (PD), tremor, dystonia, refractory epilepsy, chronic pain, depression and obsessive compulsive disorders. It should appeal to anyone training or working in the healthcare arena - whatever their particular discipline - who wants either a concise introduction to the subject, or a gentle reminder of stuff they might have forgotten. We have aimed the book at:

- Movement disorder neurologists, movement disorder specialist nurses, epileptologists, epilepsy specialist nurses, and residents in neurology.
- Pain specialists, pain specialist nurses and residents in pain management.
- Physicians of all grades who care for patients with PD, tremor, dystonia, chronic pain, or any patients who had a neurostimulator implanted.
- Psychiatrists and psychiatric specialist nurses with an interest in treatment refractory depression and OCD, and residents in psychiatry.
- Neurosurgeons interested in neurostimulation and neurosurgical residents.
- Any healthcare professional interested to learn more about neurostimulation.

This book is divided into sections on deep brain, motor cortex, vagus nerve, spinal cord, and peripheral nerve stimulation. Each section covers approved and emerging applications with chapters on each diagnosis and target to make it easier for healthcare professionals to navigate the text quickly to the desired information.

*Neurostimulation: Principles and Practice* is a systematic approach to understanding the mechanism of action, rationale, indications, patients’ selection, targets, and programming of neurostimulators using common sense and the art of applying scientific knowledge to practice. No attempt is made to give detailed descriptions of surgical methods used to implant neurostimulators; these surgical methods have been adequately described in stereotactic books written specifically to neurosurgeons specializing in functional neurosurgery.
Contributors to this book were selected from around the globe because of their expertise and knowledge of each subject.

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Part 1
Deep Brain Stimulation
Chapter 1
Deep Brain Stimulation: Mechanisms of Action

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Introduction

Deep brain stimulation (DBS) is arguably the most effective treatment for movement disorders, such as Parkinson’s disease (PD) and dystonia. DBS succeeds where all manner of pharmacological and biological therapies, such as neurotransplant, fail. Further, the range of disorders amenable to DBS is expanding rapidly, for example depression and epilepsy. At first, this may seem surprising, but that one would be surprised suggests a lack of appreciation that the brain is basically an electrochemical organ. The brain processes and transmits information electrically and, consequently, it should not be surprising that the brain’s functions can be affected electrically. For example, while neurotransmitters, independently or affected by neuromodulators, result in changes in the electrical status in the post-synaptic neurons. The varying electrical changes induced by neurotransmitters are electrically integrated (processed) to produce new “information” that is subsequently encoded in the electric signal in the form of the axon potential train exiting the post-synaptic neuron. Further, changes in the neurotransmitter-induced post-synaptic electrical status produce further changes entirely independent of the neurotransmitter, such as post-excitatory depression of excitability due to deactivation of sodium (Na⁺) conductance changes or post-inhibitory increases in excitability due to activation of Na⁺ conductance channels among other voltage-sensitive conductance changes. Thus, for example, inhibition of the ventrolateral (VL) thalamus by activity in the globus pallidus interna (GPI), for many neurons results in a net increased VL neuronal activity contrary to what would be expected based on the neurotransmitter.
Neurostimulation

released by GPi neurons onto VL neurons, that being gamma amino butyric acid (GABA) [1].

There has been a neurohumoral approach (analogous to an endocrine approach in terms of relative excesses or deficiencies in neurotransmitters or other chemical substances) to explain behavior since antiquity [2], and this was greatly reinforced with the discovery of neurotransmitters [3], the equating of neurotransmitter properties with electrical properties, and the rapid advances in pharmacology. Nevertheless, it would be an error of the category type (equating apples and oranges) derived from the fallacy of pseudo-transitivity (assuming similarity in one domain implies similarity in another domain) to equate neurotransmitter physiology to neurophysiology.

For example, the leading theories of basal ganglia pathophysiology and physiology focus on the GABAergic inhibition of the VL neurons. PD has been associated with overactivity of the GPi (falsely). The observation that destructive lesions of the GPi improved PD led to the false claim that similar benefits means that high-frequency DBS reduces activity in the GPi, via the fallacy of pseudo-transitivity. It is now clear that GPi DBS does not inhibit activity in GPi as measured by microelectrode recordings within the GPi or in VL thalamus [1,4]. Similarly, subthalamic nucleus (STN) DBS does not inhibit the output of the STN [5,6]. Recordings in VL thalamus do show a reduction in VL neuronal activity in the 3.5–7 ms following a GPi DBS pulse, but this is followed by a rebound in VL thalamic activity, such as through the thalamic neuron I_h channels and probably by reentrant feedback from the cortex [5]. For many VL neurons, GPi results in delayed increased neuronal activity, a phenomenon not accounted for in most theories of PD pathophysiology. Certainly, this effect on VL neurons could not have been predicted by what is known about GABA. Thus, the neuronal physiology is not synonymous with neurotransmitter function. It is my opinion that while the neurochemistry and molecular biology of the basal ganglia have advanced rapidly, the understanding of the neurophysiology of the basal ganglia, more properly considered as the basal ganglia-thalamic-cortical system, has not. In large part this lack of progress in neurophysiology is that neurohumoral explanations have been thought sufficient.

Despite the remarkable advances in the clinical application of DBS since its first description in its modern form by Dieckmann for psychiatric disorders in 1979 [7] and by Cooper et al. for movement disorders in 1980 [8], little is known about the mechanisms of action of DBS. The lack of understanding of the mechanisms of action is not for lack of studies. A PubMed search on “mechanism” and “DBS” results in 235 citations. To be sure, many have suggested a variety of possible mechanisms; however, most are inconsistent with much of the experimental observations or do not or cannot provide a precise causal chain of events from injection of electrical charge into the brain with each DBS pulse to the behavior of motor units (the combination of a lower motor neuron and the muscle fibers it innervates).

This chapter begins with an attempt to answer the question as to what is the fundamental mechanism by which the DBS injection of electrical charge
affects neurons. The implications of that answer for certain theories of DBS therapeutic mechanisms will be explored.

**Importance of pathophysiological theories**

Examination of the mechanisms of action of DBS did not and does not occur in a vacuum. Indeed, the popularization of DBS in the late 1980s and early 1990s despite the first use of DBS as it is done now in 1979 [7] and 1980 [8] is in large part due to the development of certain theories regarding the pathophysiology of movement disorders, particularly PD [9]. Indeed, the nature of theories of Parkinson pathophysiology current at the time directly shaped inferences as to DBS therapeutic mechanisms based on clinical effects. Later the prevailing theories of pathophysiology would shape what DBS experiments would have to be done, and what results were relevant and irrelevant as evidence. Indeed, it was the latter that was responsible for many errors in early DBS research resulting from confirmation bias.

The problem here is that it is very difficult to discuss DBS mechanisms without discussing the pathophysiological theories of the relevant neurological disorders that provides the context for DBS research. Indeed, these theories follow long antecedent conceptual approaches dating back to at least Aristotle. However, a full discussion is beyond the scope of this effort but this author’s perspective has been published elsewhere [10,11,12,13,14]. Consequently, only specific aspects can be addressed here to provide some context to the issues related to DBS mechanisms.

**The neuronal response to deep brain stimulation**

This section surveys research observations regarding how individual neurons respond to the DBS pulse. A distinction is made between neuronal responses and neural responses. The former relates to individual neurons while the latter refers to the response of networks of neurons. This distinction is particularly important in view of the importance of DBS frequencies on therapeutic effects of DBS. As will be shown, the individual neuron’s response to each DBS pulse is relatively the same despite DBS frequency, as shown in Figure 1.1 [5]. Consequently, the properties of the individual neurons are not likely to be the primary determinant of DBS because the frequency of DBS does have a specific effect on symptoms and the fact that the neuronal responses are the same means that the explanation of dependence on DBS frequencies for the therapeutic effect cannot be explained at the neuronal level. It is most likely that neural responses, that is the effects percolated throughout the basal ganglia-thalamic-cortical system are most relevant. Nevertheless, the neural network depends on driving activities within neurons; hence it is important to understand how neurons respond to DBS.
As described earlier, the early theories of the therapeutic DBS mechanisms were inferred from the similarity of clinical efficacy of GPi and VL DBS to pallidotomy and thalamotomy, respectively. Thus, high-frequency DBS was thought to inhibit neuronal activity while low-frequency excites. As shown in Figure 1.1, this is not the case. However, as luck would have it, early neurophysiological studies appeared to provide support. Benazzouz et al. [15] recorded in the substantia nigra pars compacta while stimulating the STN in rodents and because they were unable to remove stimulus artifact, they studied the neuronal activity immediately following a DBS train of pulses. There was a reduction in neuronal activity, which was inferred to reflect activity during stimulation, which is now known to be a false inference. Recordings in the GPi with STN DBS demonstrate increased neuronal activity.
during stimulation with a profound reduction of GPi neuronal activity following cessation of DBS [5].

Most inferences of neuronal effects are related to direct microelectrode recordings. However, such recordings are highly selective of action potentials generated in the soma (cell body) and dendritic tree. Microelectrode recordings often demonstrated a reduction in extracellular action potentials in the stimulated target, with the inference that this was reflective of neuronal activity in general. This could reflect a tendency to think of a neuron primarily in terms of the soma and dendrites without appreciating the role of the axon. However, McIntyre and Grill [16] demonstrated, based on biophysical modeling, that action potentials could be generated in local axons despite reduced ability to generate action potentials in the soma and dendritic tree. Supportive neurophysiological observations in animals were rediscovered [17,18]. In addition to the biophysical explanation of reduced somatic and dendritic action potentials, it also was suggested that activation of pre-synaptic terminals, which have the lowest threshold to stimulation, resulted in somatic and dendritic hyperpolarization as the majority of pre-synaptic terminals are mediated by neurotransmitters that cause hyperpolarization in the post-synaptic neuron. Alternatively, some pre-synaptic neurotransmitters result in “shunting” inhibition in the soma and dendrites, rather than hyperpolarization, and have demonstrated reduction in action potentials in the soma and dendrites despite generation of action potentials in the axons [19].

Consequently, a therapeutic effect of DBS related to reduction in somatic and dendritic activity versus axonal output, for example in the STN, could not be distinguished. However, subsequent studies of therapeutic STN DBS demonstrated antidromic activation of the contralateral STN in patients whose ipsilateral PD symptoms were not worsened with STN DBS [20,21]. Consequently, STN overactivity is not a sufficient cause of PD nor is reducing STN neuronal activity a therapeutic mechanism of DBS (previous studies have shown that STN DBS activity is not greater than that recorded in the STN of patients with epilepsy and hence increased STN activity is not a necessary condition of PD [22]).

There is considerable evidence that DBS activates axons in the vicinity of the stimulating electrodes, whether they terminate in the stimulated target or are passing through the target. Evidence includes demonstrations of antidromic activation of cortical neurons with STN DBS [5,21] in response to STN DBS as well as in VL neurons in response to GPi DBS. Thus, it is entirely possible that the therapeutic effects of DBS may not have anything to do with activations of local neurons [23].

Another interesting phenomenon is that DBS is inefficient in activating neurons. For example, only on the order of 10–20% of DBS pulses result in an antidromic response [1]. The question is whether such inefficiencies are necessary for the DBS therapeutic effect. The hypothesis is that a certain degree of inefficiency is optimal for the DBS effect [12]. For example, some have argued that increasing DBS frequency or electrical current (voltage)
results in a worsening effect on clinical symptoms. The precise mechanism is not clear; however, the explanation that spread to the internal capsule, at least in the case of STN DBS is not likely [12]. The hypothesis offered is that DBS resonates, and, hence, amplifies, neuronal activity within the basal ganglia-thalamic-cortical system in order to increase the signal-to-noise ratio to improve PD symptoms. In this case, the signal is the modulation of neuronal activity over time. However, there is a narrow range in which resonance would work. Insufficient activation of neurons will not amplify the signal. However, excessive driving of neurons will dampen the modulation by a ceiling effect.

DBS also synchronizes neuronal responses (Figure 1.1) as neurons have relatively stereotyped repetitive responses to the DBS pulses. Thus, DBS does not desynchronize neuronal activity within the basal ganglia-cortical system as some have suggested. Further, recordings of motor unit activity (the summed muscle action potentials or muscle fibers simultaneously driven by an individual lower motor neuron) demonstrate synchronization with the DBS pulse [24]. Thus, if lower motor neurons are driven to synchronization with the DBS pulse, then it is very likely that the upper motor neuron in the motor cortex likewise is driven to synchronization with the DBS pulse. Whether or not this synchronization is due to antidromic activation of motor cortex neurons in the case of STN DBS [25] or by orthodromic activation accompanying antidromic activation of VL thalamic projection neurons is unknown.

The notion that DBS should desynchronize neuronal activities is derived by inverse inference that PD is consequent to abnormal synchronization of neuronal activities within the basal ganglia [26,27]. Further, computational simulations reinforced this notion. This suggests two caveats. First, inferring from the inverse is very problematic and may lead to false conclusions. Second, computational simulations often utilize powerful optimizing techniques. The consequence would be demonstration of plausible biological mechanisms that are not remotely true. Further, the misleading nature of computational simulations demonstrates the critical need for sufficient biological data to constrain the computational simulations.

To summarize the effects of DBS on neurons, the primary effect is depolarization of the neuronal membrane, which if the depolarization reaches threshold, an action potential is generated. Different neuronal elements have different thresholds. The lowest threshold is found in the pre-synaptic axonal terminals, the next lowest threshold is at the action potential initiating segment at the axon hillock or first inter-node, followed by the axon, and then finally by the soma and dendrites (some dendrites are capable of generating action potentials in terms of propagating regenerating changes in neuronal membrane potentials). Thus, perhaps the predominant effect is activation of pre-synaptic axonal terminals in the vicinity of the DBS electrodes and simultaneously, generation of action potentials of axons in the vicinity of the DBS electrodes. As many, if not most, pre-synaptic terminals release inhibitory neurotransmitters, the initial effect may be hyperpolariza-
Deep Brain Stimulation: Mechanisms of Action

Deep Brain Stimulation: Mechanisms of Action

The observations described earlier, call into question whether or not the direct neuronal responses to DBS are what mediate the therapeutic effects. The alternative is that it is the neural effects, meaning activations of the basal ganglia-thalamic-cortical system, that are required to effect the therapeutic response. Unfortunately, the vast majority of studies of DBS mechanisms have been confined to the stimulated target or structures monosynaptically downstream of the neurons within the stimulated target. The exception is a study in non-human primates with STN DBS-like stimulation, which demonstrates that the DBS-induced activity percolates through the entire basal ganglia-thalamic-cortical system (Figure 1.1). Further, these effects persist on the order of several milliseconds beyond the DBS pulse. Neither antidromic nor monosynaptic orthodromic mechanisms would explain the time course of the neuronal responses. Clearly, there is some additional means beyond direct driving by the DBS pulse that is determining the pattern of neuronal responses. A neural (polysynaptic) mechanism is most likely.

Further evidence of neural or network mechanisms underlying therapeutic DBS in the case of Parkinson’s disease comes from evidence that DBS virtually anywhere within the basal ganglia-thalamic-cortical system is effective. For example, DBS of the Gpi, GPe [28], VL, STN, motor cortex [29,30], and putamen [31] improve parkinsonian symptoms. Either there are as many therapeutic DBS mechanisms as there are targets or there is a single (or relatively few) and, consequently, the DBS is a system effect and not a structure effect. A system effect is more consistent with a neural response to DBS.

The systems oscillators theory posits that the basal ganglia-thalamic-cortical system can be conceived as a system of dynamically coupled re-entrant polysynaptic oscillators with non-linear properties (so as not to confuse with continuous harmonic oscillators), schematically represented in Figure 1.2 [13]. The system is made up of many oscillators of different lengths; hence, different inherent frequencies. The repetitive pulses of the DBS train interact via resonance, both positive and negative. Resonance of different oscillators within the basal ganglia-thalamic-cortical system with different DBS frequencies mediates the clinical responses to DBS of different frequencies [13].
The concepts suggested by the Systems Oscillators theory are very different from current oscillator-based theories of PD pathophysiology, such as the beta oscillation theory [5,10,11,13,32]. This theory posits increased neuronal activity in the beta frequencies (8–30 Hz) as causal to PD. To be sure, increased power in the beta frequencies are seen in local field potentials recorded in various basal ganglia nuclei [33] which is reduced with levodopa administration or STN DBS. Similarly, DBS in the beta frequencies has been described as worsening PD symptoms, presumably by increased neural oscillations in the beta frequency. Consequently, DBS has been postulated to improve PD by reducing beta oscillations.

Figure 1.3 shows the hand opening and closing amplitudes and frequencies for a patient with STN DBS for PD at different DBS pulse rates [34]. As can be seen, there are multiple peaks in the amplitude and frequency, and DBS in the lower range of the beta frequencies improved motor performance. DBS in the higher beta frequencies did not worsen motor performance. Thus, the presence of beta oscillations, presumably resulting from DBS in the beta frequencies, is not a sufficient cause of PD, otherwise there would have been worsening of the PD symptoms.

Further, most studies of beta oscillations in local field potentials report composite or averaged data; in those few that show individual data there are some patients who do not display increased power in the beta oscillations. This demonstrates that increased beta power is not a necessary condition...
Deep Brain Stimulation: Mechanisms of Action

for PD because there are subjects who clearly have parkinsonism but do not have increased power in the beta frequencies. As beta oscillations is neither a necessary nor sufficient condition, it must be epiphenomena, in which case reduction in beta oscillations cannot be causal to PD, and thus, reduction of beta oscillations is not a therapeutic mechanism of action for DBS.

The results shown in Figure 1.3 suggest that improvements in hand opening–closing are improved at multiple but distinct frequencies. Second, the DBS stimulation rates that improve amplitude are not necessarily the same for hand opening–closing frequency suggesting different mechanisms, although what these mechanisms might be remains unknown. However, if DBS acts via resonance with ongoing oscillations within the basal ganglia-thalamic-cortical system, then the multiple peaks in improved motor performance suggests that there are multiple oscillators within the basal ganglia-thalamic-cortical system, as predicted by the systems oscillators theory, corresponding to the DBS frequencies associated with the peaks in the motor performance.

If the multiple peaks in motor performance associated with specific DBS rates are indicative of multiple and, consequently, independent oscillators within the basal ganglia-thalamic-cortical system, the question becomes what are the mechanisms that underlie these different oscillators and what are their specific roles in the function of the basal ganglia-thalamic-cortical system. At this point, one can only speculate and this is beyond the scope

Figure 1.3  Mean relative amplitudes of the thumb and finger movements during a repetitive hand opening–closing task. The mean amplitudes were from three trials at multiple subthalamic nucleus deep brain stimulation (DBS) frequencies. As can be seen, there are multiple distinct peaks over a wide range of frequencies, including in the beta range.
of this chapter, but there is a theory [13]. There is evidence that DBS does interact with oscillators within the basal ganglia-thalamic-cortical system. For example, as discussed above, STN DBS generates antidromic action potentials in the contralateral STN but only a fraction of the DBS pulses result in an antidromic action potential. Further study demonstrated that the antidromic action potentials were not random but periodic at 27 and 67 Hz, with many neurons showing both 27- and 67-Hz oscillations in the antidromic responses [35]. This suggests that the antidromic responses depend on the neuronal membrane potential and that the membrane potential oscillates at 27 and 67 Hz. As the 27 and 67 Hz are not commensurate (their ratio results in an irrational number), these oscillations must represent separate mechanisms. Further, the phase of the oscillations is different among STN neurons simultaneously recorded, suggesting that they represent different oscillators though at the same frequency.

It is likely that these oscillations at 27 and 67 Hz reflect polysynaptic reentrant neural oscillators, which are loosely coupled and non-linear. These mechanisms are feasible as demonstrated by mathematical simulations [36]. Assuming a conduction and synaptic delay between an action potential in one neuron and an increase in the membrane potential in the post-synaptic neuron (whether directly excitatory or post-inhibitory) of 3.7 ms, a 27-Hz oscillator suggests a 10-neuron (or node) oscillator within the basal ganglia-thalamic-cortical system. A 67-Hz oscillator suggests a four-neuron (or node) oscillator, such as motor cortex to putamen to GPi to VL back to motor cortex or a motor cortex to STN to GPi to VL and back to motor cortex.

Interestingly, STN DBS on the order of 67 Hz does not appear to improve motor performance (Figure 1.3), whereas DBS at twice that frequency appears optimal for motor performance. There are at least two possible explanations. First, it is possible that the STN DBS interacts with a two-neuron (or two-node) oscillator, such as the motor cortex-VL thalamus oscillator or the GPi-STN oscillator. Studies of VL neurons in response to GPi DBS may demonstrate such a phenomenon [5]. GPi DBS results in antidromic activation of VL neurons (Figure 1.4) [1]. This is followed by a reduction in VL neuronal activities consistent with activation of GPi axons projecting to the VL thalamus. This is followed by a slight rebound, though above pre-stimulation levels, which in turn is followed by a dramatic increase in activity at approximately 5 ms following the DBS pulse. However, there are subtle but telling changes in the antidromic and late activations. The late activations clearly can be seen to build, but at the same time there is a reduction in the antidromic response. There are at least two explanations. First, there is a build up of hyperpolarization in the VL neuron that blocks the antidromic activation, but this is not seen in the baseline activity that immediately follows where the antidromic response would have been. Alternatively, there may have been an action potential in the VL neuron (undetectable because it coincides with the stimulus artifact) that “collides” with the antidromic response, thereby preventing an action potential in the soma and dendritic tree of the VL neuron and, thus, no recordings of extracellular action potentials. This