

Part 1

Deep Brain Stimulation

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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

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.

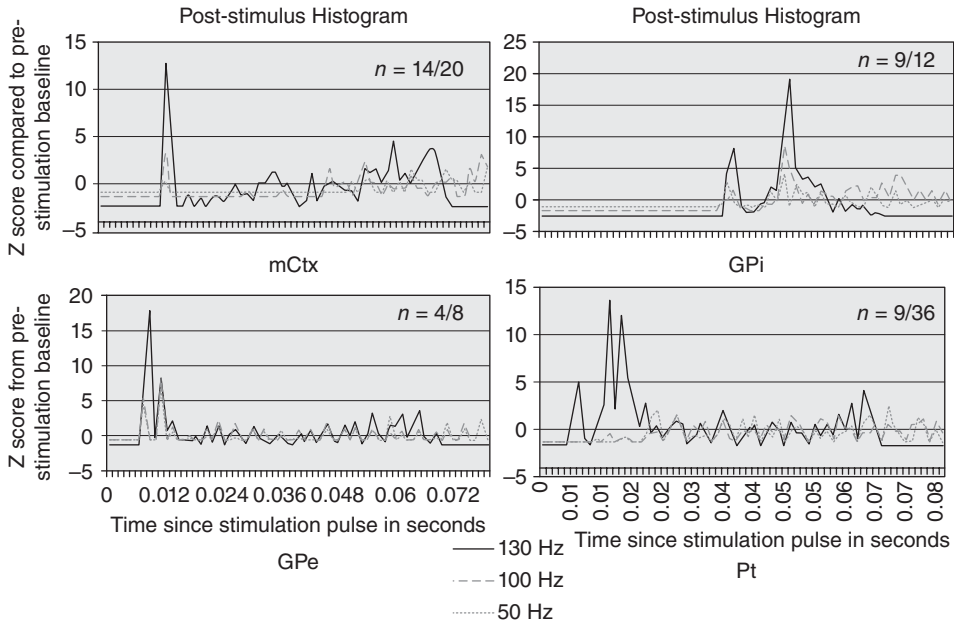


Figure 1.1 Post-stimulus histograms showing the changes in neuronal activity in the mCtx (motor cortex), globus pallidus interna (GPi), globus pallidus externa (GPe) and putamen (Pt) over the time interval from the onset of the subthalamic nucleus deep brain stimulation (DBS) pulse (time 0) to 8 ms after the DBS pulse (which is the interpulse interval for the 130pps DBS). The ratio show the number of neurons demonstrating this pattern out of the total number of neurons recorded in that structure. The magnitudes of histograms have been z-score transformed and thus are in units of the value minus the mean of the pre-stimulation baseline divided by the standard deviation of the pre-stimulation baseline. As can be seen, the qualitative response in these neurons are relatively the same regardless of DBS frequency. However, there are quantitative differences in the magnitudes. The DBS frequencies typical of those clinically effective are associated with a greater magnitude of response. Reproduced from [13] with permission from Informa Healthcare.

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-thalamic-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-

tion of the somas and cell bodies in the vicinity of the DBS electrodes. This would be detected as a loss of action potentials recorded within the DBS target implying an inhibitory DBS effect. However, action potentials are generated in efferent axons such that the net effect is activation of the output of the stimulated structure. Recent evidence suggests that activation of the efferent axons is primary to the DBS effect and not the effect on the soma and dendrites of the DBS target. Generation of action potentials in the efferents of the DBS target then percolates throughout the network and it is this effect on the network that most likely is causal to the DBS therapeutic effect.

Neural responses to deep brain stimulation

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].

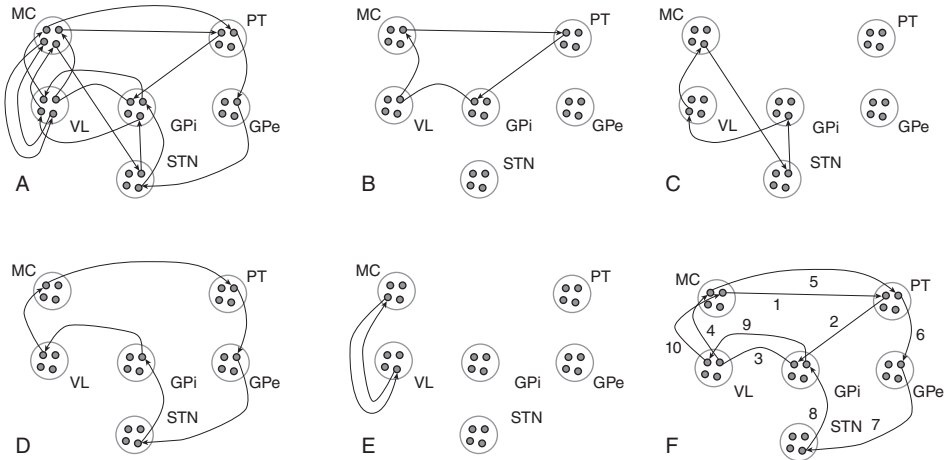


Figure 1.2 Schematic representations of the anatomical interconnections of some of the structures (A) within the basal ganglia-thalamic-cortical system where MC is the motor cortex, PT is putamen, GPe is globus pallidus externa, GPi is globus pallidus interna, STN is subthalamic nucleus, and VL is ventrolateral thalamus. Subsets of interconnections represent different possible oscillators (B-F) with different lengths represented by the number of nodes (collections of neurons) in the different structures. The different lengths result in different inherent or fundamental frequencies. Reproduced from [13] with permission from Informa Healthcare.

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 (8-30Hz) 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

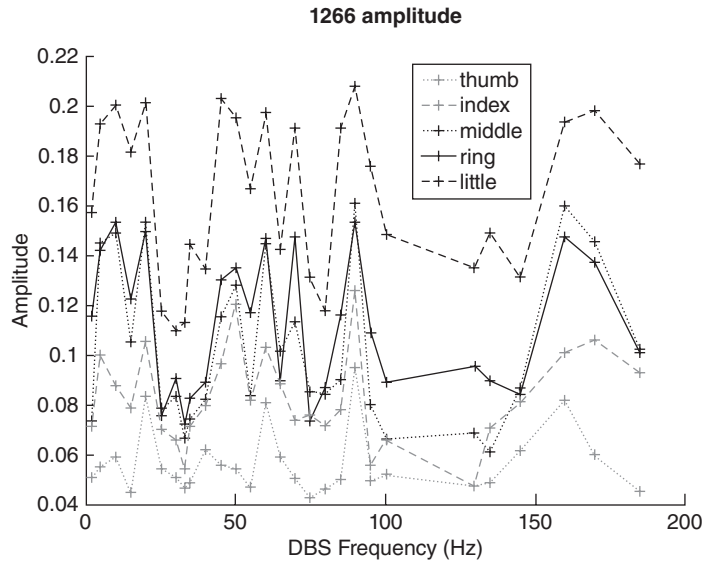


Figure 1.3 Mean relative amplitudes of the thumb and finger movements during a repetitive hand opening-closing task. The mean amplitudes were from three trials at multiple subthalamic nucleus deep brain stimulation (DBS) frequencies. As can be seen, there are multiple distinct peaks over a wide range of frequencies, including in the beta range.

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

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

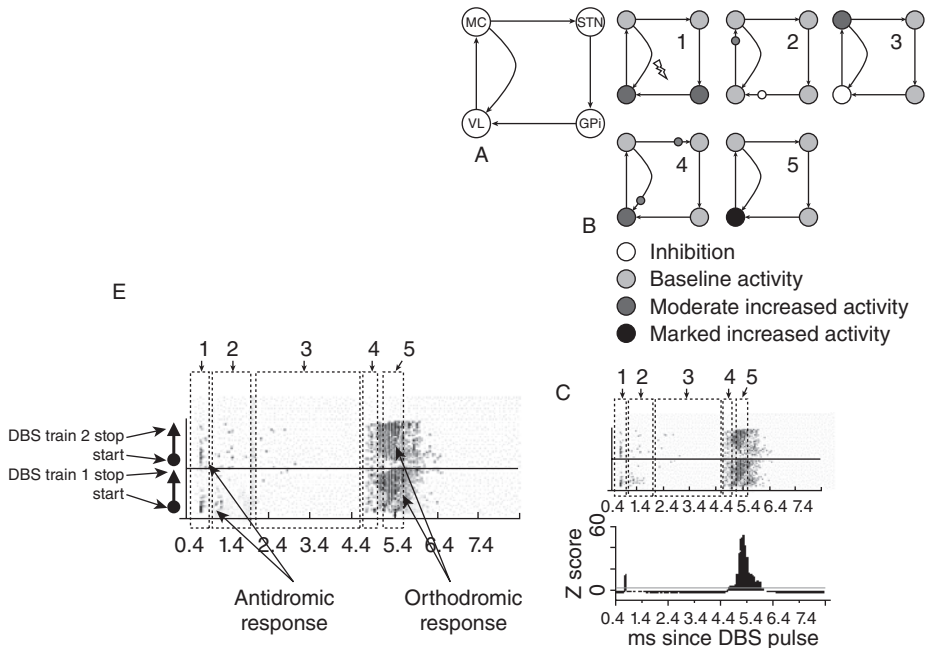


Figure 1.4 Example of post-stimulus rasters and histograms of the response of a ventrolateral (VL) neuron to globus pallidus interna (GPI) deep brain stimulation (DBS). E and C are rasters where each dot represents the discharge of a VL neuron during the inter-DBS pulse interval during high-frequency DBS. Note there are two separate trains of DBS (E). Each row represents the response to a single DBS pulse. The raster is “collapsed” by combining rows to produce the histogram seen in the bottom of C. As can be seen, there is a highly temporally consistent peak at approximately 0.8 ms following the DBS pulse consistent with antidromic activation (zone 1). There is a subsequent return of activity (zone 2) to baseline. At approximately 3.5 ms there is a reduction below baseline consistent with activation of GPI action potentials that then cause hyperpolarization of the VL neuron (zone 3). This is followed by a rebound increase in activity above baseline thought to represent post-inhibitory rebound excitability (zone 4). Later, there is a marked increase in neuronal activity (zone 5) thought to reflect feedback from activation of cortical neurons (most likely motor cortex (MC in A)). Evidence of a feedback mechanism is the progressive build up of the late response in zone 5; at the same time there is a reduction of the antidromic activity (zone 1). The most likely mechanism for reduction in the antidromic response is collision where an orthodromic action potential in the VL neuron, probably from the motor cortex, creates a refractory period that blocks an antidromic action potential from reaching the VL soma and dendrites where it could be recorded from the microelectrode in VL. This mechanism is schematically represented in A and B. A DBS pulse causes activation of the VL to motor cortex axon that results in an antidromic action potential being detected in the VL neuron (B1) and simultaneously, an orthodromic activation of the cortical neurons (B2 and B3). A few milliseconds later, the axonal activation of the GPI neuron results in release of GABA onto the VL neuron resulting in a reduction of activity (B2 and B3). At this time, the orthodromic activation of the motor cortex results in an action potential in motor cortex neurons (B3) that later results in orthodromic activation of the VL neurons (B5).

would explain why there is a progressive loss of antidromic responses as the late response builds, if one assumes that the late response is due to feedback from the motor cortex.

However, this would not explain the benefit of STN DBS at 250Hz (not shown) in the hand opening-closing experiments described earlier, which would be too fast for any polysynaptic oscillator. Alternatively, supraharmonic DBS of a neural oscillator is effective for reasons that are unclear. One possible explanation is that the subsequent DBS pulse at 250Hz falls on the post-refractory period increased excitability, for example due to activation of I_h channels or the greater activation of Na^+ channels induced by the prior pulse. Thus, a resonance amplification at the site of activation on the neuron could be related to the improvement of motor performance at 250-Hz DBS.

Higher order effects of deep brain stimulation

Whatever the therapeutic mechanisms of action of DBS for motor effects, it must correct the underlying abnormality in motor unit orchestration. The problem is that these abnormalities of motor unit control in movement disorders, such as PD, are poorly understood. Indeed, they are not understood because prior theories of basal ganglia pathophysiology never considered it necessary to explain motor unit control. Most theories posited that motor unit control was related to the biophysical properties of the lower motor neurons and thus, not affected by suprasegmental structures, such as the basal ganglia.

It is now clear that the abnormalities associated with motor unit control go far beyond simple one-dimensional push-pull dynamics of either general increases or decreases of motor unit activity. The Size Principle, which relates to the orderly recruitment of progressively larger motor units with increased force requirements, is abnormal and even reversed in some patients with PD [37]. In rapid movements, the relationships between the initial increase and then decrease in agonist electromyography, followed by an increase then decrease of antagonistic muscles, which in turn is followed by a final increase in the agonist muscle represents another higher level of motor unit orchestration that is abnormal in PD and current theories of PD pathophysiology, and therapeutic DBS mechanisms do not begin to explain these abnormalities.

The hypothesis offered here

Space limitations necessitate only a brief description of the alternative Systems Oscillators theory to explain basal ganglia pathophysiology and the therapeutic effects of DBS. Further explication and discussion of evidentiary support is offered elsewhere [5,10,11,13]. The basic premise is that the basal

ganglia-thalamic-cortical system is organized as numerous loosely coupled oscillators (Figure 1.2). The oscillators are constructed from reentrant connections between neurons. The nature of the interconnections is non-linear, which makes the oscillators discrete non-linear in contrast to typical harmonic continuous oscillators. The nodes of the oscillators comprise a subset of neurons within each of the nuclei and cortex of the basal ganglia-thalamic-cortical system. Thus, there may be many oscillators involved in given nuclei or cortex and the same neurons of a node may participate in multiple oscillators. Thus, an individual neuron may participate in multiple oscillators. Each neuron within a node does not discharge with each cycle of the oscillator but acts as a rate divider. Thus, the discharge activity of a neuron is less than the frequency of the oscillator in which it is embedded.

Because the oscillators are discrete, by virtue of the neurons in the node, they are discontinuous because of state changes that are different degrees of excitability and refractoriness. Similarly, thresholds from converting from continuous fluctuations in the membrane potential as inputs to discrete “all-or-nothing” action potentials at outputs mediated, conveys one aspect of non-linearity.

The discrete states and non-linear translations within the neurons confer unique properties on the basal ganglia-thalamic-cortical network, particularly related to interactions between oscillators. First, neurons of such systems are capable of simultaneously entraining multiple oscillators. Each oscillator serves as a carrier frequency to entrain information. The different frequencies of oscillations are related to a specific function that operates over a specific time scale. For example, the disinaptic VL motor cortex oscillator operates at high frequencies, approximately 147 Hz and, thus, can drive motor unit discharges at very short time scales. Conversely, the side-loops through the basal ganglia operate at lower frequencies to encode behaviors of a larger time scale, for example the temporal organization of agonist-antagonist-agonist muscle activations described earlier [13].

DBS acts as another oscillator within the basal ganglia-thalamic-cortical system. It acts as a loosely coupled oscillator because of the relative ineffectiveness of each DBS pulse to elicit an action potential [1]. Had the effectiveness been greater, the DBS would no longer act as a loosely coupled oscillator which would greatly change the dynamics within the basal ganglia-thalamic-cortical system [12]. In addition, the DBS oscillator is discrete because the DBS pulse, that is the time period by which it interacts with the other oscillators within the basal ganglia-thalamic-cortical system, is very brief relative to the interstimulus pulse interval.

The DBS oscillator then interacts with the basal ganglia-thalamic-cortical system depending on its frequency. For example, when the DBS oscillator is commensurate with specific basal ganglia-thalamic-cortical oscillators (which means that the ratio of their frequencies does not result in an irrational number), there can be interactions between these oscillators. However, if the DBS frequency is incommensurate with the frequency of a given oscillator the interaction becomes problematic or impossible.

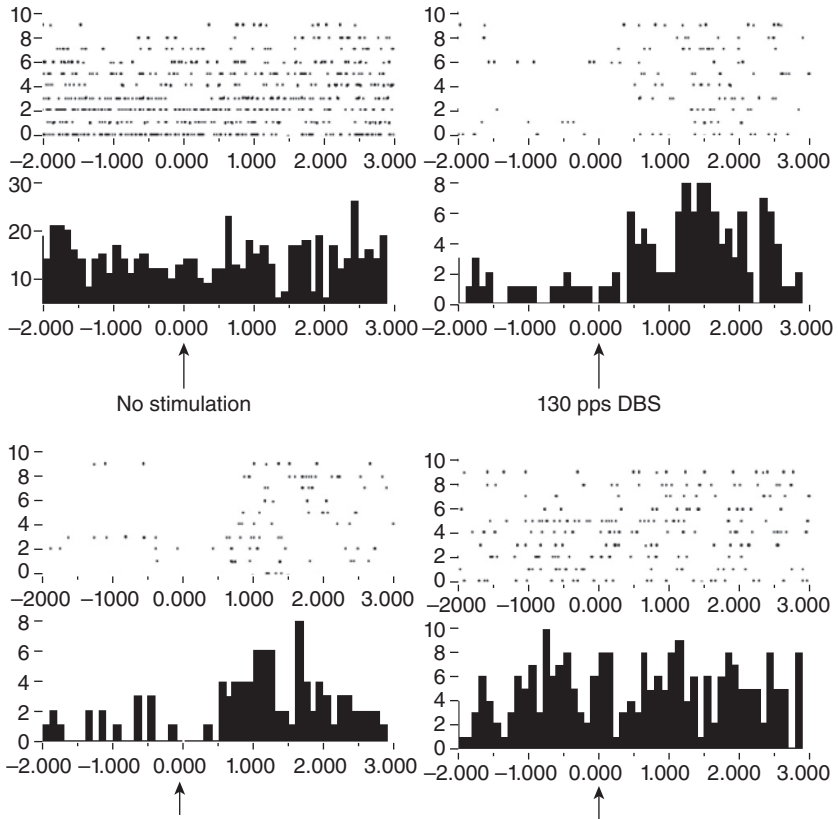


Figure 1.5 Peri-event rasters and histograms of a putamen neuron's activity in a non-human primate with a DBS-like system implanted in the subthalamic nucleus. The animal was trained to make an arm-reaching task in response to a go signal that occurred at time 0 and indicated by the upward arrow. The top of each figure shows rows of dots where each dot represents the discharge of the neuron. Each row represents the activities during a single trial of the task. The time scale is from 2 s before to 2 s after the go signal. The bottom parts of each figure are histograms from collapsing the rows above. As can be seen, under the no DBS condition, there is very little modulation of the neuronal activity relative to the go signal. At high frequency DBS, 130 pps, there is a remarkable modulation of the neuronal activity demonstrating the involvement of this neuron in task performance. At lower frequency DBS there is less modulation of neuronal activities. It is not likely that high-frequency DBS created the modulation of the neuronal activity as the DBS pulse train is constant. More likely, is that the modulation, representing a signal or information, was present but lost in the background activity. One possibility is that DBS at the proper frequency causes a resonance amplification of the underlying signal. Reproduced from [5] with permission from Elsevier.

The Systems Oscillators theory holds that the DBS pulse train can interact via positive and negative resonance to affect information encoded by the neuronal activities. Figure 1.5 demonstrates the effects of positive resonance on neuronal activity in the putamen. The converse, that is suppression of information also has been demonstrated and suggests that one action of DBS is to suppress misinformation [5].

The observations and hypotheses offered above present a novel conception of higher-level disorders in neurological and psychiatric disease. By higher level it is meant anything other than paralysis, in the case of movement disorders. This conception is that higher-level disorders are disorders of information causing misinformation rather than a loss or suppression of information. For example, the GPI rate theory posits that overactivity of the GPI in parkinsonism suppresses movement or blocks what would otherwise be normal information from reaching the motor cortex for subsequent expression.

Information implies a temporal dynamic, that is the modulation of neuronal and neural states over time. Further, the time scales over which information is encoded is on the order of milliseconds. For example, the difference in the structure of a therapeutic DBS at 150 pps and an ineffective DBS at 100 pps is an approximately 3.3ms difference in the inter-DBS pulse intervals. Further, the relevant time scales are multiple and over a wide range as inferred from the multiple frequencies associated with the effects of STN DBS on hand opening-closing. It is highly unlikely that the one-dimensional push-pull dynamics that underlie much of the thinking about mechanisms of neurological and psychiatric disease and correspondingly about the mechanisms of DBS will provide anything close to a satisfactory explanation. Clearly, there must be an iterative process where explorations of DBS mechanisms cause changes in theories of pathophysiology, which in turn will affect the interpretations of DBS mechanisms. However, this will necessitate a revolutionary reassessment of modes of thinking going back to Aristotle [14]. At the very least, the therapeutic efficacy of DBS clearly re-establishes the primacy of the electrophysiological nature of brain function.

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