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Review

Mechanisms of action of deep brain stimulation (DBS)

Erwin B. Montgomery Jr[a,*], John T. Gale[b]

[a]*Department of Neurology, National Primate Research Center, University of Wisconsin–Madison, H6/538 CSC, 600 Highland Ave., Madison, WI 53792, USA*
[b]*Department of Neurosurgery, Massachusetts General Hospital/Harvard Medical School, Edwards Research Building, EDR 410, 50 Blossom St., Boston, MA 02114, USA*

Abstract

Deep brain stimulation (DBS) is remarkably effective for a range of neurological and psychiatric disorders that have failed pharmacological and cell transplant therapies. Clinical investigations are underway for a variety of other conditions. Yet, the therapeutic mechanisms of action are unknown. In addition, DBS research demonstrates the need to re-consider many hypotheses regarding basal ganglia physiology and pathophysiology such as the notion that increased activity in the globus pallidus internal segment is causal to Parkinson's disease symptoms. Studies reveal a variety of apparently discrepant results. At the least, it is unclear which DBS effects are therapeutically effective. This systematic review attempts to organize current DBS research into a series of unifying themes or issues such as whether the therapeutic effects are local or systems-wide or whether the effects are related to inhibition or excitation. A number of alternative hypotheses are offered for consideration including suppression of abnormal activity, striping basal ganglia output of misinformation, reduction of abnormal stochastic resonance effects due to increased noise in the disease state, and reinforcement of dynamic modulation of neuronal activity by resonance effects.

Keywords: Basal ganglia; Deep brain stimulation; Movement disorders; Parkinson's disease; Dystonia; Neurophysiology; Pathophysiology; Subthalamic nucleus; Globus pallidus

Contents

*Corresponding author. Tel.: +1 608 263 5420; fax: +1 608 263 0412.
E-mail address: montgomery@neurology.wisc.edu (E.B. Montgomery Jr).

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1. Introduction

Despite of the fact that there is no clear understanding of the therapeutic mechanisms of action of deep brain stimulation (DBS), it is highly effective in the treatment of an increasing array of neurological and psychiatric disorders. Already considered standard and accepted treatment for Parkinson's disease (Deep Brain Stimulation in Parkinson's Disease Group, 2001), Essential tremor (Koller et al., 1997), dystonia (Yianni et al., 2003), and cerebellar outflow tremor (Montgomery et al., 1999), clinical trials are underway for epilepsy (Loddenkemper et al., 2001), depression (Stefurak et al., 2003), obsessive-compulsive disorder (Abelson et al., 2005), and minimally conscious states (Yamamoto et al., 2005). Clearly, clinical developments in the past did not require a detailed knowledge of the neuronal mechanisms of DBS but at the minimum, notions as to the mechanisms have inspired or given confidence to pursuing new clinical applications. For example, the early notion that DBS inhibits the stimulated target nucleus thereby, reducing what was considered overactivity in the target, had considerable heuristic value. Thus, DBS of the globus pallidus interna (GPi) has replaced pallidotomy. Extending this notion further, DBS of the anterior limb of the internal capsule may replace capsulotomy for obsessive-compulsive disorder.

The remarkable effectiveness of DBS must be saying something about the underlying neuronal pathophysiology. For example, DBS for Parkinson's disease is effective when all manner of medications (Deep Brain Stimulation in Parkinson's Disease Group, 2001) and indeed, when brain fetal dopamine cell transplantation fails (Olanow et al., 2003). Clearly, DBS must be addressing neuronal pathophysiological mechanisms not addressed by pharmacological or cellular replacement of dopamine. The success of DBS in the face of pharmacological and cellular transplant failure and the expansion of DBS to other clinical conditions give considerable confidence that a greater understanding of the therapeutic mechanisms of action will lead to even more effective therapies for a wider array of neurological and psychiatric disorders.

Expanding use of DBS has resulted in a number of inconsistencies and paradoxes that may require a fundamental reconsideration of current hypotheses of DBS mechanisms of action and suggests benefit in considering a wider range of perspectives, which is the purpose of this review. Contrary to earlier notions that only high frequency DBS was clinically effective, recent studies demonstrate that low frequency DBS, in some circumstances such as the pedunculopontine (PPN) nucleus for gait disorders (Stefani et al., 2007) or of the STN for speech (Wojtecki et al., 2006) in Parkinson's disease. The same high frequency DBS of the GPi is effective for both hypokinetic disorders, such as chorea (Montgomery, 2004a,b), as well as hypokinetic disorders such as Parkinson's disease (Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001). This is inconsistent with current theories that hold that the mechanisms underlying hypo- and hyperkinesia are reciprocal. DBS of nearly every nuclei in the basal ganglia-thalamic-cortical (BG-Th-Ctx) system is effective for at least some symptoms of Parkinson's disease, for example GPi (Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001), STN (Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001), ventrolateral thalamus (VL) (Koller et al., 1997), globus pallidus external segment (GPe) (Vitek et al., 2004), and motor cortex (Canavero et al., 2002). The putamen (Pt) is not listed only because the authors are unaware of any attempts at putamenal DBS, not that it has been shown not to work. Either there are as many different DBS mechanisms as there are effective targets or there is some common mechanism that is not unique to any particular target. This suggests that it may be profitable to view DBS from a "systems" perspective rather than just its local effects, an approach that here-to-fore has not been received much consideration.

At the minimum, a better understanding of how DBS works may shed considerable light on the neuronal pathophysiology of diseases such as Parkinson's disease and perhaps illuminate our understanding of normal brain physiology. In this regard, the current interest in DBS mechanisms is timely because current notions of basal ganglia pathophysiology, particularly as it relates to Parkinson's disease, are in a state of flux. First, as will be discussed, therapeutic high frequency DBS of GPi and STN directly increases GPi output (Hasmimoto et al., 2001; Anderson et al., 2003; Montgomery, 2006), which is inconsistent with current theories positing GPi overactivity as causal to Parkinson's disease (Albin et al., 1989; DeLong, 1990). Second, GPi activity does not solely inhibit VL neurons, many demonstrate post-inhibitory rebound increased excitability sometimes causing net increases in neuronal activity over baseline with GPi DBS (Montgomery, 2006). In addition, GPi DBS probably antidromically activates VL neurons that result in orthodromic activation of cortical neurons. Third, recent studies demonstrate that the pattern of DBS and not just the frequency is important for its therapeutic effect (Ma and Wichmann, 2004; Montgomery, 2005). Thus, a better understanding of DBS mechanisms of action increases it utility as a probe to study brain function.

Demonstration of the importance of the pattern of DBS is particularly interesting in view of recent interest in abnormal oscillations within the basal ganglia as a potential pathophysiological mechanism, particularly in Parkinson's disease. Basal ganglia oscillations in local field potentials in the 11–30-Hz range are thought antikinetic (Brown, 2006; Brown and Williams, 2005; Hutchison et al., 2004) as evidenced by reductions in STN oscillations in this frequency range are correlated with improvement (Kuhn et al., 2006). DBS in this frequency range worsens motor performance (Fogelson et al., 2005a,b). Oscillations in the range of 70 Hz are thought to be prokinetic, because they

are lost in PD (Hutchison et al., 2004; Pogosyan et al., 2006) and restored with levodopa treatment (Fogelson et al., 2005a,b).

The relevance of oscillators in Parkinson's disease to DBS is illustrated in the following case report of a single human undergoing DBS demonstrating the importance of DBS patterns (unpublished observations). This patient had a STN DBS lead placed but required revision of the DBS lead because of previous placement of the extension connector in the neck which was subsequently shown to increase the risk of DBS lead fractures. During the surgery, it was possible to connect the lead to an external stimulator (Grass Instruments S88 with dual SIU7 stimulus isolation units) under computer control. This experiment received prior Institutional Review Board (IRB) approval and informed consent by the patient.

Constant current and charge-balanced stimulation with pulse width for each phase of 0.9 ms were delivered under computer control. The authors evaluated motor function of the contralateral upper extremity while blinded to the pattern of stimulation. Five different patterns were used all at the same overall frequency of 130 (pulses per second) pps. There was 130 pps regular and 130 pps irregular with the inter-stimulus intervals drawn randomly from a Gaussian distribution. Another set of stimulation patterns was modulated stimulation were the instantaneous stimulation frequencies varied regularly from 6 to 256 pps. The rates of these variations were 2, 5 and 10 Hz for different stimulation periods.

Fig. 1 shows the effects of these stimulation patterns on finger tapping in the ipsilateral and contralateral hand as measured by the motor examination of the unified Parkinson rating scales (UPDRS). The graph in Fig. 1 shows the change in finger tapping scores from the pre-stimulation baseline. The order of the different stimulation patterns was randomized. As can be seen, DBS at 130 pps resulted in an improvement in the finger tapping performance, while stimulation with 130 pps irregular caused a worsening of finger tapping performance. However, DBS at 130 pps modulated at 2 Hz produced the greatest worsening of motor performance followed by 130 pps modulated at 5 Hz and then 130 pps modulated at 10 Hz. While this is only a single case, the results are intriguing and hopefully this study will be expanded by future research. But it does raise the question about what kind of effect is inherent in the 130 pps DBS modulated at 2 Hz compared to the 130 pps irregular DBS.

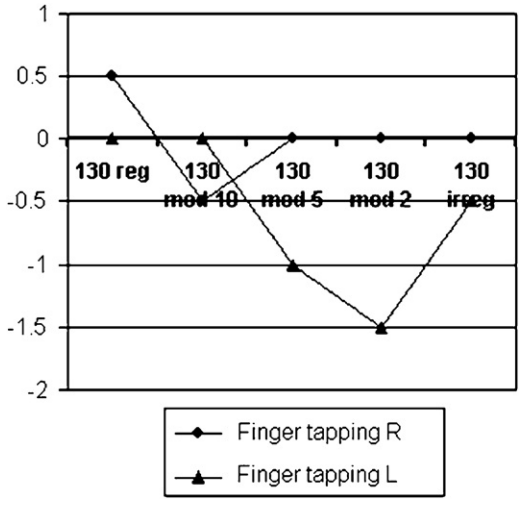


Fig. 1. Changes in the Unified Parkinson disease rating scale for finger tapping in the left hand contralateral to the DBS lead and to the ipsilateral hand (right) in a single subject with Parkinson disease and STN DBS. The evaluator was blinded to the pattern of stimulation. The 130 pps DBS modulated at 2 Hz worsened motor performance (negative change in score), but regular DBS at 130 pps improved motor performance. Irregular DBS at 130 pps average did not have a marked effect.

Given the state of uncertainty as to the pathophysiological mechanism, the importance of a better understanding of the pathophysiology for the development of new treatments, and the potential insights that DBS research may contribute, a critical review of the current state of understanding of DBS mechanisms is important as this paper attempts. However, perhaps more important at this stage of understanding, or lack thereof, is the necessity to consider a wide variety of hypotheses and possibilities, if for no other reason than to stimulate debate and subsequent research. Such hypotheses, given the current state of knowledge, necessarily will be speculative and often based on "work in progress" and indulgences are appropriate. The premature windowing of possibilities and considerations seems unwise.

DBS and its mechanisms of action have captured the imagination of many scientists as evidence by the abundance of papers published. It is not feasible to recognize all the important contributions by these scientists in this review. Further, our goal in this review was not to catalogue the many contributions but rather to synthesize the important themes. Consequently, we have cited only a limited number of studies that represent or typify certain themes. In addition, our laboratory has focused on relatively novel themes. These are the effects of DBS throughout the basal ganglia-thalamic-cortical (BG-Th-Ctx) system and the importance of the DBS pulse train rather than the response to individual pulses. Most other laboratories examine the effects of individual DBS pulses and assume that these responses generalize to the effects of a DBS pulse train. Much of the work from our laboratory is preliminary and in need of repetition, verification, and extension. However, the uniqueness of those observations, their contrast to much of the current published work, and timeliness of these issues justifies their presentation.

The central themes to be addressed include: (1) whether DBS inhibits or excites the stimulated target; (2) whether the therapeutic DBS mechanisms of action are local or attributable to the basal ganglia-thalamic-cortical system (BG-Th-Ctx); and (3) whether the effects follow from responses to a single pulse or a collective of pulses. Possible therapeutic mechanisms, from the review of the literature and data, have been distilled and synthesized into key

hypotheses which include: (1) Direct Inhibition Hypothesis; (2) Indirect Inhibition of Pathological Activity Hypothesis; (3) Increased Regularity of GPi and Reduced Miss-information Hypothesis; and (4) Resonance and Carrier Signal Effect Hypothesis. Which of these or their variations or some entirely novel hypothesis emerges as the most plausible awaits further research.

2. Inhibition or Excitation

One of the first controversies, which persist, is whether high frequency DBS inhibits the stimulated target. Originally, the hypothesis of inhibition was based on the similarity of clinical efficacy with ablation and high frequency DBS. Just as thalamotomy and pallidotomy improved parkinsonian symptoms so did thalamic and pallidal DBS, respectively. Unfortunately, this analogy constitutes a logical fallacy. If curare and stroke equals paralysis, this does not mean that curare and stroke have the same mechanism. While a number of brain imaging studies, such as cerebral blood flow or 2-deoxyglucose metabolism studies demonstrate similar changes with pallidotomy and pallidal stimulation, the fundamental issue of logic still pertains whether the similarities are clinical or brain imaging. Further, surgical ablation and DBS are not synonymous. Lesions of the GPe can produce parkinsonism yet GPe DBS can reverse parkinsonism (Vitek et al., 2004).

The notion that DBS inhibits the stimulated target, particularly in the context of GPi and STN DBS, has considerable appeal in that it resonated with current theories of Parkinson's disease pathophysiology. The hypothesized overactivity of GPi indirectly due to overactivity of the STN (Albin et al., 1989; DeLong, 1990) provided a strong rationale why local inhibition of GPi or STN should be therapeutic. DBS direct inhibition of overactivity constitutes the Direct Inhibition Hypothesis.

As luck would have it, some initial studies did demonstrate a reduction of neuronal activities in neurons receiving input from the stimulated target. Stimulus artifact in early studies required examination of neuronal activity following cessation of stimulation with the presumption that neuronal activity seen immediately following stimulation would be representative of neuronal activity during stimulation (Benazzouz et al., 2000). The reduction in activity of (substantia nigra pars reticulata (SNpr)) with STN stimulation was inferred to be the result of decreased STN output. However, it is not necessarily the case that what happens after stimulation reflects what occurs during stimulation. High frequency DBS of the STN in a non-human primate demonstrates increased activity during stimulation utilizing computer algorithms to remove stimulus artifact as shown in Fig. 2 (Montgomery et al., 2005). Interestingly, in this example, there is a marked reduction in neuronal activity following discontinuation of the STN DBS. Therefore, one cannot extrapolate from what happens following DBS to what occurs during DBS.

Subsequent studies used dual microelectrodes in the same structure, one for stimulating and the other for recording adjacent neuronal activity. These studies did demonstrate a reduction in GPi neuronal activity with microstimulation in GPi (Dostrovsky et al., 2000). However, these studies used stimulation frequencies less than typically used in therapeutic DBS in order to avoid loss of signal due to stimulus artifact. Other studies also have demonstrated reduced activity or blocked pathological within the target stimulated such as thalamus (Kiss et al., 2002) and STN (Filali, 2004; Garcia, 2003; Magarinos-Ascone et al., 2002; Tai et al., 2003).

A number of mechanisms have been proposed to explain how DBS can reduce neuronal activity within the stimulated target (Lozano and Eltahawy, 2004). These include depolarization blockage, neurotransmitter depletion (Iremonger et al., 2006) and stimulation of pre-synaptic terminals with neurotransmitter release. Given the very large predominance of inhibitory pre-synaptic terminals in the STN and GPi, their release by DBS locally could reduce neuronal activity within the stimulated target (Lee et al., 2004). Biophysical analysis confirms that pre-synaptic terminals are most sensitive to electrical stimulation (Rattay, 1998). Computational modeling also has demonstrated that DBS may hyperpolarize local neuronal cell bodies and dendrites (McIntyre and Grill, 1999; McIntyre et al., 2004).

The inherent assumption of the above experiments by Dostrovsky et al. (2000) and others (Garcia, 2003; Kiss et al., 2002; Magarinos-Ascone et al., 2002; Meissner et al., 2005; Tai et al., 2003) is that what occurs local to the DBS

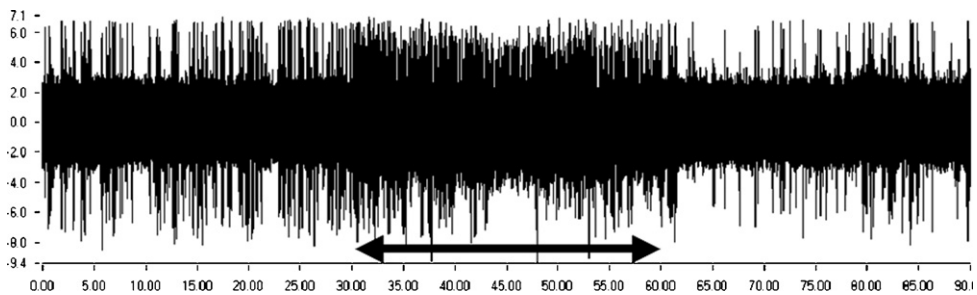


Fig. 2. Multi-unit recording of GPi neurons during 30 s before, during (indicated by the horizontal arrow) and after STN DBS. Note the increased activity followed by a reduction (Montgomery, 2003).

is relevant to the therapeutic mechanisms of action. When the focus is shifted to downstream structures that receive inputs from the DBS target structures, the picture is very different. A large number of studies including microelectrode recordings of neuronal activities in downstream structures have consistently demonstrated changes indicative of activation of outputs from the stimulated structures. Anderson et al. (2003) demonstrated predominant decreases in VL activity with GPi stimulation consistent with activation of inhibitory projections from GPi to VL. These findings were confirmed in similar recording from human VL neurons during GPi DBS. In this case, 25 neurons all showed a reduction in neuronal activity at a latency of approximately 3 ms following the GPi DBS pulse and lasted approximately 2.5 ms (Montgomery, 2006). Hashimoto et al. (2003) and Gale and Montgomery (2003) have demonstrated increased GPi activity with STN DBS consistent with activation of excitatory projections from STN to GPi. Metabolic studies in rodents demonstrate increased neurotransmitter and second messenger release in structures downstream of the DBS target in rodents (Windels et al., 2000) and humans, respectively (Stefani et al., 2005). Also, PET blood flow imaging demonstrated findings consistent with activation of thalamic outflow with thalamic DBS (Perlmutter et al., 2002).

Are the findings of local inhibition but outflow excitation irreconcilable? Computation modeling suggests a resolution. McIntyre and Grill demonstrated that stimulation could hyperpolarize the cell body and dendrites yet still excite an action potential at the axon initial segment or proximate inter-nodes (McIntyre and Grill, 1999; McIntyre et al., 2004). There also is neurophysiological evidence of such phenomena (Coombs et al., 1957; Llinas and Terzuolo, 1964; Steriade et al., 1974).

If both inhibition and excitation coexist then which is therapeutically relevant? From a systems perspective it would seem that activated output would trump local inhibition. But there is some empirical evidence that bears on the question. If there is an example where DBS of a structure did not have the same effect as ablation, then DBS and ablation are not equivalent. Lesions of the GPe can produce parkinsonism yet GPe DBS can reverse parkinsonism (Vitek et al., 2004). At least in this case the possible local inhibition of GPe by DBS cannot explain the therapeutic efficacy of GPe DBS. Further, clinical studies suggest that DBS in the white matter above the STN is therapeutically effective (Lanotte et al., 2002; Voges et al., 2002; Yokoyama et al., 2001). It is unlikely that direct DBS effects would inhibit axons.

In reality, the question of DBS effects is more complicated than simple excitation or inhibition. A number of investigators have demonstrated complex patterns of both inhibition and excitation (Bar-Gad et al., 2004; Hashimoto et al., 2003; Montgomery, 2006). Interestingly, many studies demonstrated increased activity approximately 5–7 ms following the STN DBS pulse in GPi (Gale, 2004; Hasmimoto et al., 2001), VL thalamus (Gale, 2004), GPe (Gale, 2004), and Pt (Gale, 2004) and in GPi (Bar-Gad et al., 2004) and VL thalamus (Montgomery, 2006) with GPi stimulation. This is particularly interesting because the inter-stimulus interval of therapeutic DBS is approximately 5–7 ms. This provides a mechanism where the latter effects of the preceding DBS pulse could interact with the immediate effects of the subsequent pulse suggesting a resonance effect (see below). The question of the origins of these complex responses remains. Are these complex responses due to local mechanisms intrinsic to the structure stimulated or the result of network interactions?

3. Local versus Systems Effects.

The large majority of other laboratories have focused on the DBS effects at the site of stimulation (Anderson et al., 2006; Bar-Gad et al., 2004; Dostrovsky et al., 2000; Filali et al., 2004; Garcia et al., 2003; Kiss et al., 2002; Kita et al., 2005; Magarinos-Ascone et al., 2002; Tai et al., 2003) or the first order neurons immediately downstream of the stimulated target (Anderson et al., 2003; Hashimoto et al., 2003; Iremonger et al., 2006; Kita et al., 2005; Maurice et al., 2003; Tai et al., 2003; Montgomery, 2006). Likewise, computational modeling have focused on local effects (McIntyre and Grill, 1999) or effects immediately down stream (Rubin and Terman, 2004). The focus on local or immediately downstream structures follows from a conceptualization of the basal BG-Th-Ctx system as a hierarchical and sequential organization of local processors (Salinas et al., 2000). However, there is empirical evidence that the BG-Th-Ctx system acts more as a parallel and distributing system (Montgomery and Buchholz, 1991). Consequently, focus on local versus immediate downstream effects of DBS still may be too narrow.

The question is whether downstream effects from DBS can be percolated throughout the entire basal ganglia-thalamic-cortical (BG-Th-Ctx) system and the therapeutic mechanism of action is a systems effect. There is some data in favor of a systems effect. DBS of the STN (Deep Brain Stimulation in Parkinson's Disease Group, 2001), GPi (Deep Brain Stimulation in Parkinson's Disease Group, 2001), GPe (Vitek et al., 2004), VL thalamus (Koller et al., 1997), PPN (Plaha and Gill, 2005; Stefani et al., 2007) and motor cortex (Canavero et al., 2003) are all effective for at least some symptoms of Parkinson's disease. Logically there are either as many different mechanisms of action as effective sites or a mechanism of action common to DBS at all sites. Occam's razor or the Law of Parsimony would favor the latter.

Studies of VL neurons in response to GPi DBS also demonstrate findings consistent with antidromic activation of VL neurons as shown in Fig. 3 (Montgomery, 2006). Criteria for antidromic activation include high fidelity of responses to stimulation, short and consistent latencies, and collision. The latter phenomenon occurs when a spontaneously occurring action potential just prior to the stimulation results in a refractory period that blocks the

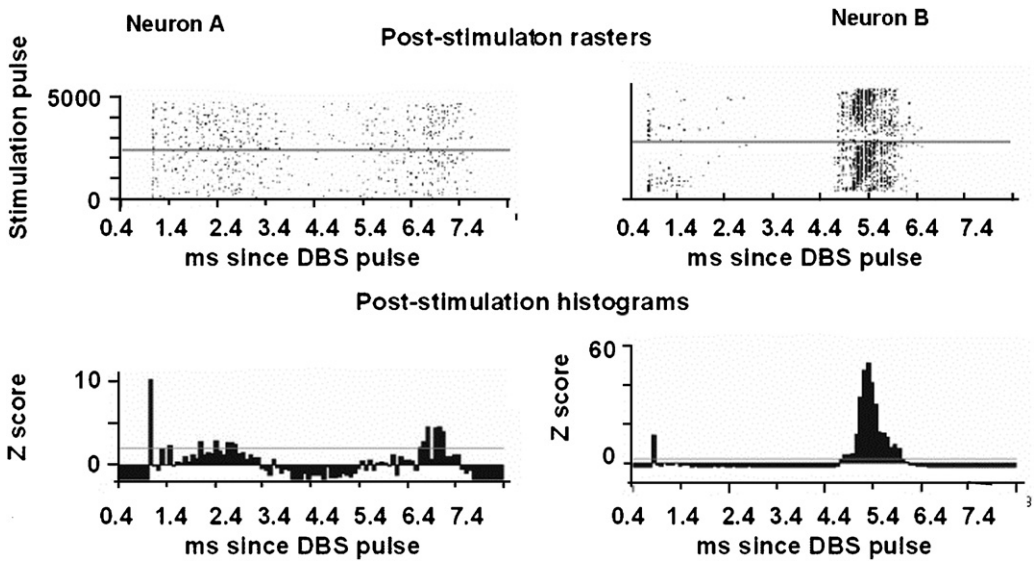


Fig. 3. Post-stimulus rasters and histogram of a VL neuron. The GPi stimulation pulse occurs at time zero. The duration of the rasters and histograms (A and B) is the inter-stimulus interval. In the raster (A) each row represents a single inter-stimulus interval and each dot represents a neuronal discharge. The rows are then summed into columns to form the post-stimulus histogram (B). As can be seen, there is a reduction in the neuronal activity beginning at approximately 3 ms and lasting approximately 3 ms. This is consistent with activation of GPi output, which is inhibitory on the VL neuron. Also note that there is a very consistent and short latency response indicated by the dotted line square at approximately 7 ms following the stimulation pulse. The consistency and short latency is evidence though not proof of antidromic activation (Montgomery, 2006).

antidromic response. Thus, the collision phenomenon depends on the statistical probability of a spontaneous action potential just prior to the stimulation pulse. This becomes problematic when the spontaneous discharge frequency is low and when the data collection period is relatively brief relative to the neuronal discharge frequency.

In the studies of VL neuronal responses to GPi DBS (and subsequent studies to be described), the possibility of an antidromic response was not anticipated. Also, the spontaneous discharge frequency of VL neurons is low. Consequently, insufficient data was collected to conduct the collision experiments with confidence. However, 88% of the VL neuron recorded demonstrated a highly consistent response at latencies of less than 1 ms. A representative example is shown in Fig. 3. As shown in Fig. 3B, there is a very robust response in the post-stimulus histogram occurring approximately 0.6 ms following the DBS pulse. No orthodromic response could have occurred within 1 ms of the stimulation pulse. The synaptic delay due to release and diffusion of neurotransmitters in an orthodromic response would take on the order of 1 ms to occur. Second, as shown 3B, the response has a *z*-score which means an increase over the pre-stimulation discharge probability 15 times the standard deviation of the pre-stimulation baseline activity indicating high fidelity of transmission. Third, there is practically no jitter or variability in the latency of the short latency response. The slight variations seen the rasters (Fig. 3C) is related to digitization noise consequent to analog to digital conversion of 25k Hz and the variability in using thresholds for detecting the occurrence of the stimulation pulse and a neuronal spike. Finally, great care was exercised to assure that what was identified as an antidromic response was not actually stimulus artifact as shown in Fig. 4.

As VL neurons are not thought to project to GPi, the origin of antidromic activation could be stimulation of VL neuron axons projecting to Pt (McFarland and Haber, 2001) or to lateral motor cortex. The antidromic activation of VL neurons could simultaneously result in orthodromic activation of motor cortex neurons. Evoked potential and EMG studies using paired-pulse to test refractory period effects or chronaxie in humans undergoing therapeutic STN DBS have results consistent with activation of axons and therefore, a high probability of antidromic activation (Ashby et al., 1999; Baker et al., 2002). Thus, one mechanism in common to VL, GPi and STN DBS is direct, either monosynaptic orthodromic or antidromic activation of motor cortex neurons. This would be consistent with the therapeutic effect of motor cortex stimulation for movement disorders (Canavero et al., 2003).

Studies of the response of human VL neurons to GPi DBS demonstrate the possible importance of systems effects, in this case, feedback in the thalamo-cortical reentrant circuit (Montgomery, 2006). An example is shown in Fig. 5, the DBS pulse in the GPi results in an antidromic activation of the VL thalamic neuron as shown in the portion of the raster enclosed in Box 1. Following the antidromic activation, there is a return to baseline activity as shown in Box 2. This is followed by inhibition probably related to monosynaptic inhibition as shown in Box 3 and then followed by rebound increased activity as shown in Box 4. It is not likely that the rebound increased excitability shown in Box 4 of Fig. 5 is due solely to

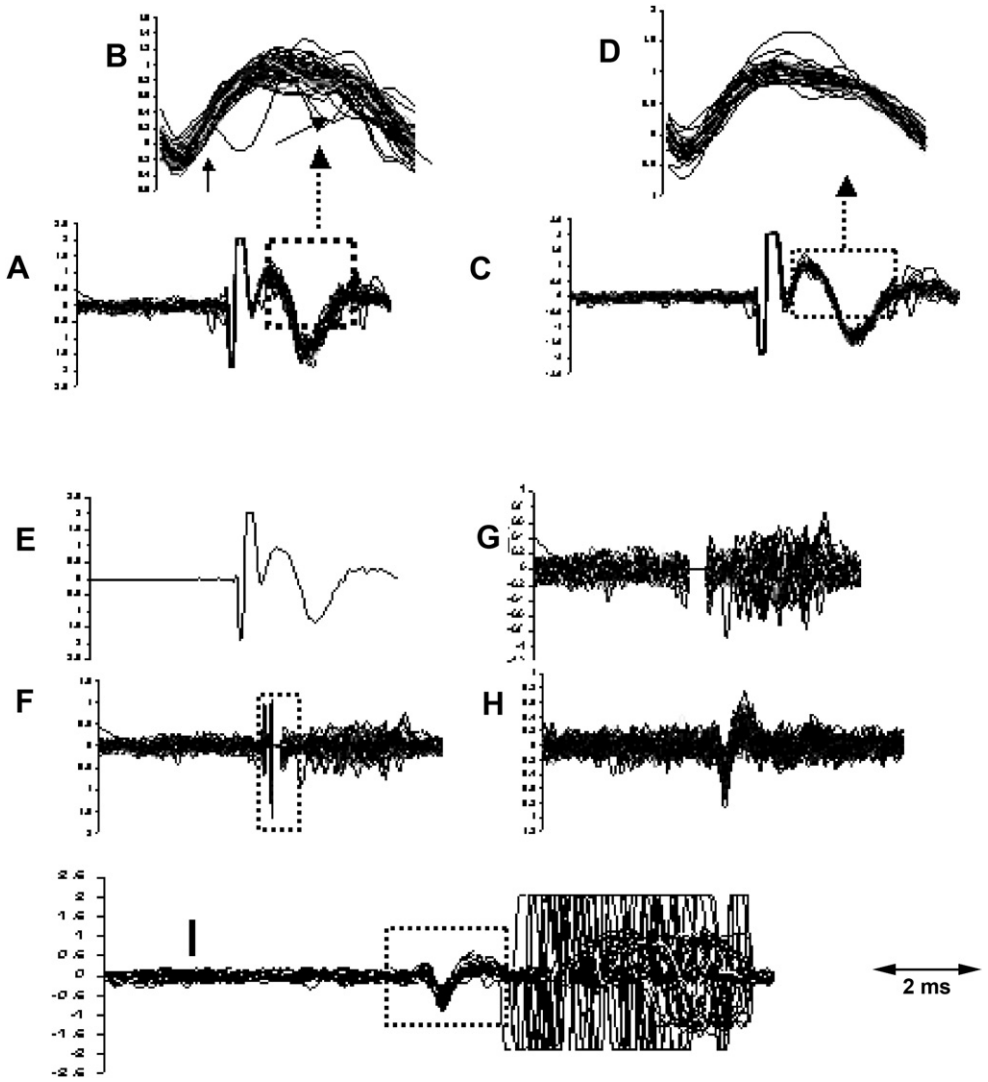


Fig. 4. An example of the results of the stimulus artifact removal algorithm to reveal short latency responses consistent with antidromic activation. Figs. A and C show superimposed segments of raw microelectrode recordings centered on the onset to the stimulus. Fig. A shows segments in which the template-matching algorithm identified waveforms referable to extracellular action potentials and Fig. C are segments in which the template-matching algorithms did not identify action potentials. As can be seen in the expanded views (B for tracings in A and D or tracings in C), there are additional waveforms contained in the slow component of the stimulus artifact for segments found to have action potentials as indicated in the solid arrows in B. These additional waveforms are not seen in D, which is an expanded segment of C. Fig. E shows the averaged evoked potential of the stimulus artifact. When this evoked potential is subtracted from the raw microelectrode recordings at the stimulus location, the slow components of the stimulus artifact are removed (F). However, the fast components remain because of slight variability in the stimulus onset. These sharp transients are removed by setting the amplitudes to zero during the sharp transients (G). As can be seen, there are a number of waveforms following the flattened segment but these are not well visualized because of the variability in the orthodromic conduction (jitter). However, the segments in G can be shifted to align the minima of the waveforms (H) revealing the waveforms of the short latency action potentials. To further demonstrate that the waveforms found embedded in the slow component of the stimulus artifact, segments of raw microelectrode recording containing identified waveforms of the action potentials occurring before the stimulus artifact were collected and superimposed in the display (I). As can be seen, the same waveform that is found embedded in the slow component of the stimulus artifact is also seen prior to the stimulus pulse. Thus, the waveforms found in the slow component of the stimulus artifact are not artifact but short latency waveforms of neuronal action potentials (Montgomery, 2006).

post-inhibitory rebound increased excitability. It is more likely, though not proven, that the post-inhibitory rebounded increased excitability must be coupled with other excitatory inputs, such as from the motor cortex, as shown in the portion of the raster enclosed in Box 5.

We studied the effects of STN stimulation on GPi, Pt, GPe, VL and cortical neuronal activity in two non-human primates (Macaca mulatta) (Gale, 2004). In motor cortex and GPe, we found very short latency (approximately 1–2 ms) highly temporally consistent robust increased neuronal activity following the DBS pulse. This is consistent with, though not proof of, antidromic activation of known projections of motor cortex and GPe to the STN based on the same criteria discussed above for VL neuronal antidromic responses to GPi DBS. We also found increases in neuronal activity in motor cortex, GPe, GPi and Pt at approximately 4–6 ms consistent with orthodromic activation. Interestingly, the increase in neuronal activity in

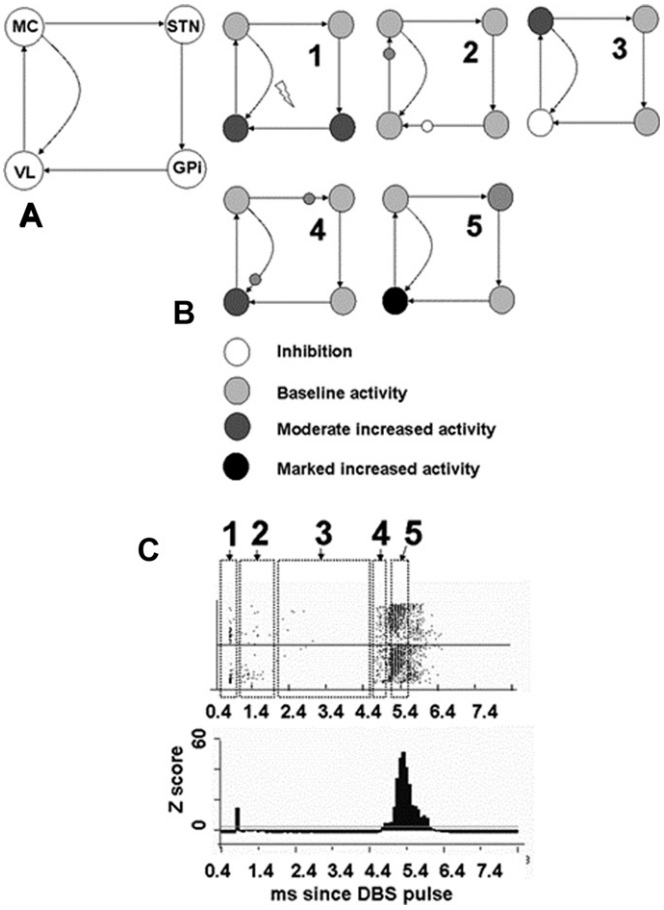


Fig. 5. Some VL neurons demonstrate a remarkable post-inhibitory rebound increased excitability (C). A potential mechanism is schematically represented (B). A nested two oscillator system is shown (A). The first oscillator is the disynaptic feedback loop between MC and VL. The second loop consists of the MC to STN to GPi to VL and then back to MC. Each numbered step (B) shows the subsequent activations beginning with the synchronized activation of VL and GPi neurons in step 1. The activity in VL is then transmitted to MC while activity in GPi is transmitted to VL in step 2. This results in excitation of MC and inhibition of VL in step 3. MC activity is then transmitted back to VL and there is a post-inhibitory rebound increased activity in VL in step 4. The excitation from MC in step 4 then combines with the post-inhibitory rebound increased excitability in VL to result in a marked increase in activity shown in step 5 modified from Montgomery (2006).

motor cortex preceded analogous increased Pt neuronal activity consistent with known projections from motor cortex to Pt. Also, there was a third time period of increased neuronal activity at approximately 7–8 ms in all these structures. This was seen with stimulation frequencies of 100 and 50 pps. These were not seen at stimulation frequencies of 130 pps because this period of increased neuronal activity corresponds to the inter-stimulus interval at 130 pps. Thus, the subsequent DBS pulse when stimulating at 130 pps would correspond to the peak in activity at 7 to 8 ms generated by the previous DBS pulse. These effects, the immediate effect of the DBS pulse and the late effect of the previous DBS pulse, could interact and summate producing a resonance effect, which could be one mechanism of DBS therapeutic effects (see below).

The patterns of responses in GPi we demonstrated with STN DBS in the non-human primate are similar to those of Bar-Gad et al. (2004). The latter authors did not offer any explanation of the mechanisms producing these patterns. In our studies, the similarities of the patterns of responses among all the nuclei of the BG-Th-Ctx system suggest that these responses may be mediated by the network rather than mechanisms intrinsic to the GPi neurons or the GPi nucleus.

4. Effects from single DBS pulse or a collective of DBS pulses

Much of neurophysiological research at the neuronal level as focused on the effects of individual stimulation pulses (Anderson et al., 2003; Bar-Gad et al., 2004; Beurrier et al., 2001; Dostrovsky et al., 2000; Garcia et al., 2003; Hashimoto et al., 2003; Kiss et al., 2002; Kita et al., 2005; Magarinos-Ascone et al., 2002; Maurice et al., 2003; Tai et al., 2003; Wu et al., 2001) rather than interactions between sequential pulses (Kita et al., 2005; Montgomery, 2004b). However, Baker et al. (2002) demonstrated very different cortical evoked potentials when using a single pulse or a train of pulses. Similarly, Kita et al., demonstrated different response in GPe to a burst of 10 stimulation pulses delivered at 100 pps in STN compared to single pulses (Kita et al., 2005). These observations suggest that the mechanisms may be different for single pulses versus trains of pulses. The therapeutic effects of a DBS pulse may depend very much on the effects of the preceding DBS pulse and so on. We demonstrated that the neuronal responses to paired-pulse STN DBS varied with the inter-stimulus pulse interval demonstrating the importance of the sequence of pulses (Gale and Montgomery, 2003) and see below. The dependence on DBS on the interactions between responses generated by succeeding DBS pulses is reflected on the effects of varying DBS frequency and pattern on clinical effects (see below).

Clinical experience demonstrates that high frequency stimulation is necessary for therapeutic STN and GPi DBS for Parkinson's disease (Rizzone et al., 2001), indeed low frequency DBS has worsened symptoms in some cases. Early theories have argued that high frequency stimulation reduced activity in the stimulated target while low frequency DBS increased activity to account for worsening of symptoms. Because the former hypothesis is no longer tenable, the latter hypothesis is suspect. We found that the pattern of neuronal responses in GPi, GPe, Pt, and cortex directly consequent to the DBS pulse were the same with 130, 100 and 50 pps DBS (Fig. 6) (Gale, 2004).

The question then is what is different about DBS at 130 pps, which is usually therapeutic, compared to 100 and 50 pps DBS which is either ineffective or possibly worsens most Parkinson disease symptoms. One possibility is that the direct effect of the DBS pulse drives activities for approximately 7–8 ms as seen in Fig. 6. When DBS pulses

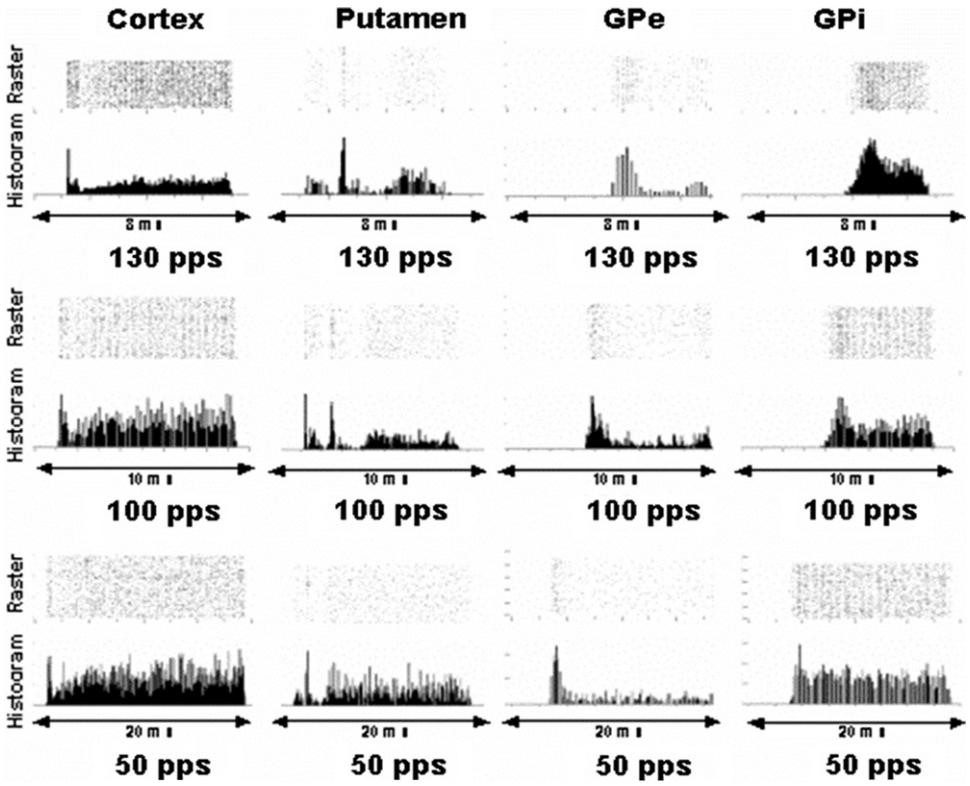


Fig. 6. Representative post-stimulus rasters and histograms of neuronal activity recorded from the cortex, putamen, globus pallidus external segment (GPe) and globus pallidus internal segment (GPi). The top portion of each figure is a raster of neuronal activity. Each dot represents the time of an extracellular action potential. Each row represents the segment of neuronal activity between each stimulation pulse. Dividing the time into bins and summing across rows results in a histogram at the lower portion of each figure. For stimulation at 130 pulses per second (pps), the time of the rasters and histograms is 8 ms; for 100 pps, it is 10 ms; and for 50 pps, it is 20 ms. As can be seen, the pattern of response in the first 8 ms the same (accounting for the compression of the time scale) regardless of the stimulation frequency.

are delivered with inter-stimulus pulse intervals less than 8 ms, such as 130 pps DBS, there is no opportunity for a return of abnormal neuronal activity. DBS at 100 and 50 pps do allow for a return of abnormal activity and therefore would not be effective. This is referred to the Indirect Inhibition of Pathological Activity Hypothesis. However, this would not explain why 50 pps DBS would worsen Parkinson disease symptoms. A second possibility is that the immediate effect of a DBS impulse combines or resonates with the late effect at 7–8 ms from the previous pulse which would occur with DBS rates at 130 pps or greater and not for DBS rates less than 130 pps. This is referred to the Resonance and Carrier Signal Effect Hypothesis.

There is evidence that the pattern of DBS in addition to frequency is important to its therapeutic effects. For example, continuous DBS at 90 pps improves motor performance compared with stimulation in cycling mode where 185 pps are delivered for 0.1 s then off for 0.1 s (Montgomery, 2005). Both continuous and cycling patterns had the same overall average stimulation rate but what differed was the pattern. The case report of the patient with Parkinson's disease with regular, irregular, and modulated STN DBS described above is another example. Further, Ma and Wichmann also demonstrated that the pattern of DBS was important, in this case a bursting pattern of DBS worsened motor performance in non-human primates (Ma and Wichmann, 2004).

5. Hypotheses of DBS Therapeutic Mechanisms

The currently popular hypothesis that STN and GPi DBS directly reduce GPi inhibition of VL, the Direct Inhibition Hypothesis, is unlikely to be true as discussed above. There are at least three viable alternative hypotheses for the therapeutic effect of DBS. First, there may be indirect inhibition of pathologic GPi activity. Second, high frequency and regular STN and GPi DBS induces regularity of GPi activity (Hashimoto et al., 2003) thereby reducing miss-information in the pathologically noisy GPi signal (Montgomery and Baker, 2002) and abnormal stochastic resonance (Montgomery, 2003). Third, high frequency and regular DBS activity induces resonance amplification of the information signals in the BG-Th-Ctx system necessary for normal movement.

5.1. Indirect inhibition of pathological GPi activity

As can be seen from Fig. 6, the first 8 ms following the DBS pulse at any frequency of stimulation is dominated by

a stereotypic response. However, after approximately 8 ms, there is a return to baseline neuronal activity, in the case of disease, a return to pathological baseline activity. Meissner et al. (2005) found similar results in STN neurons with STN stimulation. At high frequency stimulation, there is less time to return to the baseline pathological activity compared to lower frequency DBS. If one calculates the amount of returned baseline activity as a function of DBS frequency, one finds an exponentially decreasing function similar to the therapeutic effects of DBS at different frequencies (Rizzone et al., 2001). Perhaps this is one mechanism by which DBS exerts its therapeutic effect and this mechanism is referred to as the Indirect Inhibition of Pathological Activity Hypothesis.

We have very preliminary data demonstrating an inhibition of neuronal activities associated with the generation of movement in non-human primates (Gale, 2004). Fig. 7 shows a set of peri-event rasters and histograms of neuronal activity associated with an arm task. This neuron demonstrated increased activity in direct response to the DBS pulse. However, as can be seen, the normal dynamic modulation of the neuron under conditions of no DBS is not seen with DBS at 130 pps and is reduced at 100 pps and less affected by 50 pps DBS. Thus, while the direct effect of DBS is activation, there is suppression of the normal dynamic modulation with DBS at frequencies therapeutic in humans.

5.2. Increased regularity of GPi and reduced Miss-information

It is possible that the therapeutic benefit of DBS has as more to do with the regularity of DBS than the high frequency of stimulation. Empirical studies in non-human primates demonstrate that STN DBS increases the regularity of GPi neurons (Hasmimoto et al., 2001) and computational simulation of DBS also demonstrates increased regularity of GPi and VL activity (Rubin and Terman, 2004). Furthermore, both studies also demonstrate the increased regularity is associated with increase discharge rate. Interestingly, other computational simulations of information processing within simple neuronal circuits demonstrates that low frequency and irregular activity is most deleterious on information processing while high frequency and regular activity is least deleterious (Montgomery and Baker, 2000).

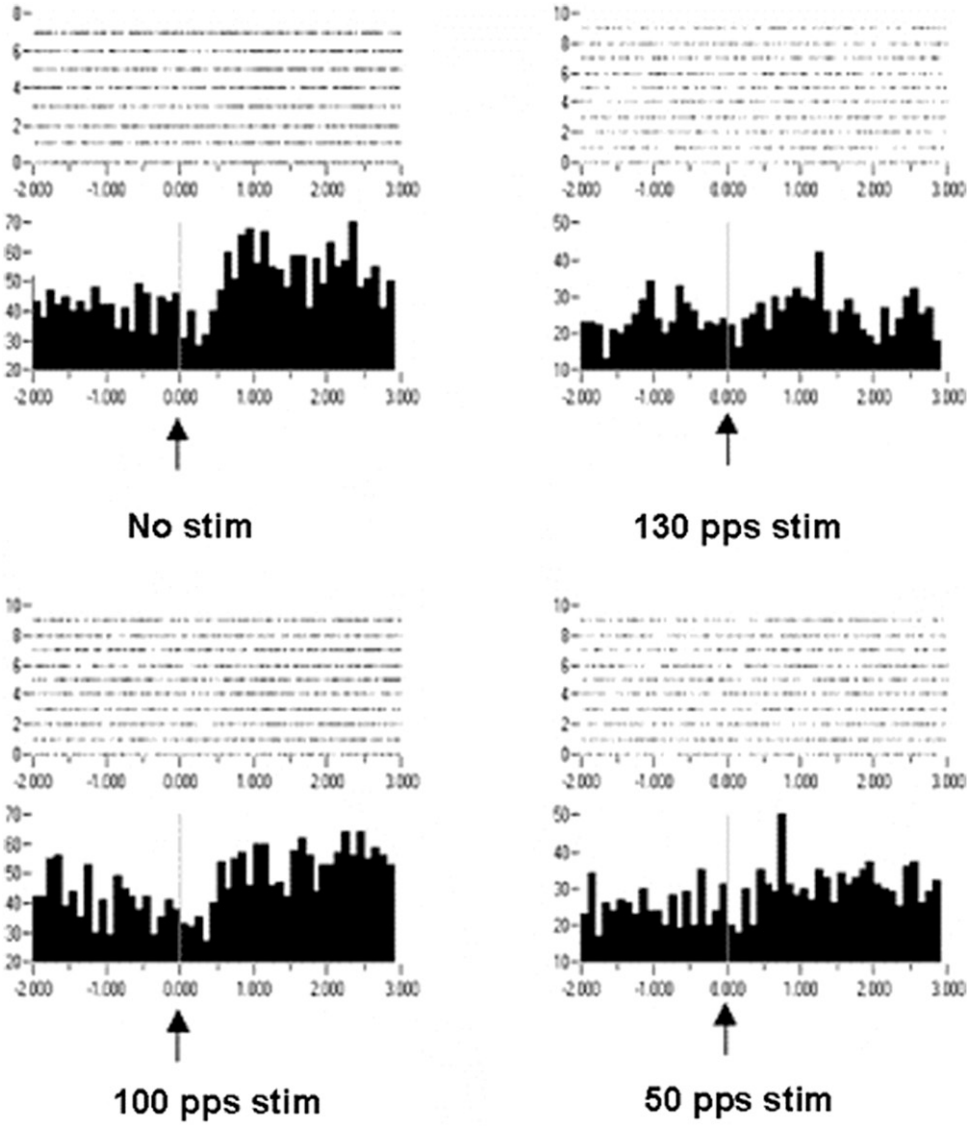
The modeling examined the efficacy of information transfer from one neuron X to a second neuron Z (Fig. 8). Neuron Z also received input from neuron Y. The information that neuron X was to convey to neuron Z was an idealized waveform that was converted to a stochastic signal. The information content in the output of neuron X was quantitated by smoothing the stochastic signal and then calculating the correlation coefficient between the idealized waveform and the smoothed stochastic output from neuron X. Neuron Z summed the activities received from both neurons X and Y. The output of neuron Z was smoothed and the correlation coefficient between the smoothed output of neuron Z and the idealized waveform was calculated. For each iteration, a positive difference in the correlation coefficient of the smoothed stochastic output of neuron Z and the idealized waveform minus the correlation coefficient between the smoothed stochastic output of neuron X with the idealized waveform represents a net gain of information. A negative difference represents a loss of information in the transfer from neuron X to neuron Z (Montgomery and Baker, 2000). A gain of information reflects stochastic resonance (Moss et al., 2004).

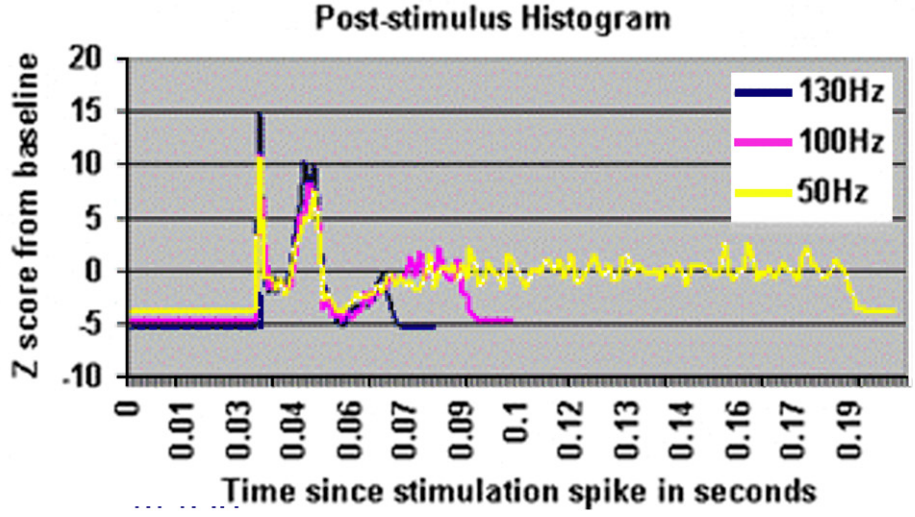
As can be seen from Fig. 9, low frequency irregular DBS caused more information loss than high frequency regular DBS. Further, high frequency irregular input causes more miss-information than high frequency regular input. In Parkinson's disease, the activity of the GPi becomes more irregular. According to the model this would cause a loss of information that could cause the negative symptoms of Parkinson's disease such as bradykinesia and akinesia. In case of Huntington's disease, levodopa-induced dyskinesia and in dystonia, GPi activity becomes lower in frequency and more irregular. This would result in a loss of information and would be expected to cause similar motor deficits to Parkinson's disease. Indeed, these patients also have bradykinesia, at least in Huntington's disease (Sánchez-Pernaute et al., 2000) and levodopa-induced dyskinesia. However, the low frequency irregular activity in the model also produces abnormal gain of information (Fig. 9). This abnormal gain of information could explain the hyperkinetic symptoms of Huntington's disease, levodopa-induced dyskinesia and dystonia. This misinformation/stochastic resonance hypothesis has the advantage of explaining DBS effects for both hypokinetic syndromes, for example Parkinson's disease, and hyperkinetic syndromes such as dyskinesia.

5.3. Resonance and Carrier Signal Effect Hypothesis

A hypothesis we offer is that high frequency DBS at 130 pps resonates with normal intrinsic oscillators within the BG-Th-Ctx system (Montgomery, 2004a,b). Indeed, there are multiple oscillators within the BG-Th-Ctx system at many different frequencies though the main or average frequency is approximately 130 pps (Gale et al., 2004). During 130 pps DBS modulated at 2 Hz, the differing inter-stimulus intervals may resonate with different oscillators. This drives the sequencing of different normal oscillators in an abnormal fashion thereby creating misinformation in the activities of the BG-Th-Ctx system.

There is intriguing though very limited and preliminary data demonstrating a possible resonance effect on dynamic modulation of neuronal activity with behavior. Fig. 10 shows a peri-event raster and histogram of the activity of a Pt neuron recorded in a non-human primate performing an arm-reaching task (Gale, 2004). Each dot in the raster indicates the time of a neuronal discharge and each row


No stim
130 pps stim
100 pps stim
50 pps stim


Post-stimulus Histogram
Z score from baseline
20
15
10
5
0
-5
-10
130Hz
100Hz
50Hz
0
0.01
0.03
0.04
0.06
0.07
0.09
0.1
0.12
0.13
0.14
0.16
0.17
0.19
Time since stimulation spike in seconds

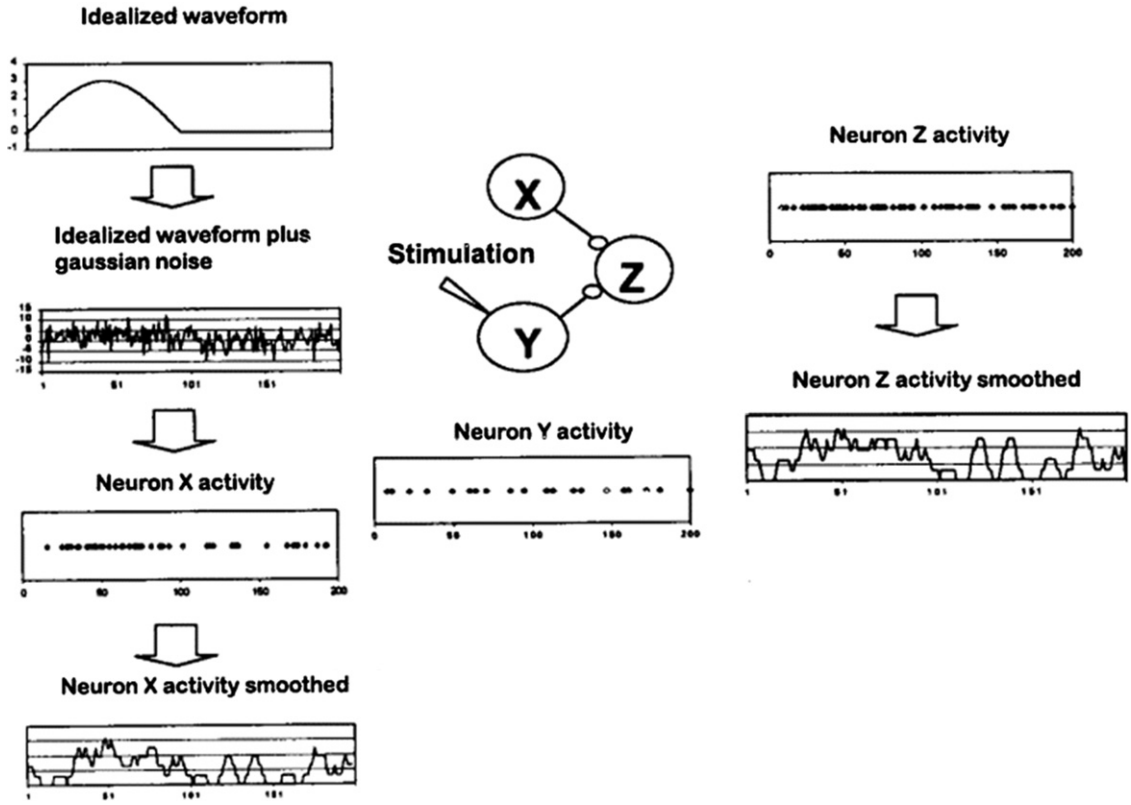


Fig. 8. Schematic representation of the modeling of information processing. The effects of activity in neuron Y, either spontaneous or in response to DBS, on information transfer from neuron X to neuron Z. See text for description (Montgomery and Baker, 2000).

represents a trial of the task. The rows are combined into columns to construct the histogram that reflects the average neuronal activity related to behavior. As can be seen, there is no modulation of neuronal activity correlated with the go signal with no stimulation. However, with continuous STN DBS at 130 pps regular, the neuron now modulates its activity with the behavior. This effect is DBS frequency dependent as there is less modulation with 100 pps regular DBS and least with 50 pps regular DBS. There are differences in the baseline activity before the go signal in the different stimulation conditions; however, there appears to be a change in the physiological functioning of this neuron with high frequency DBS. Whether this is a result of reducing the baseline so that the modulation could occur (for example, the DBS may be reducing a ceiling effect) is unknown but does not alter the conclusion. This recruitment of dynamic modulation appropriate to behavior is referred to as the Resonance Effect Hypothesis.

Evidence of resonance effects within the BG-Th-Ctx system is provided by paired-pulse experiments (Gale and Montgomery, 2003). In these studies STN DBS in two non-human primates consisted of pairs of pulses with inter-stimulus intervals systematically varied from 1 to 10 ms in 1 ms increment. Pairs of pulses were separated by, 20 ms. Post-stimulus histograms were constructed indexed to the second of the pulse pair. The post-stimulus histograms were normalized by converting the bin counts in the post-stimulus histogram to z scores based on an estimation of the bin counts from the pre-stimulation data (Fig. 11). This allowed for estimation of the statistical significance of the changes in the post-stimulus neuronal activity and comparisons across neurons with different discharge characteristics. The magnitude of the stimulation-induced changes in neuronal activities with different inter-stimulus intervals was studied.

The hypothesis is that the first stimulation pulse initiates activity within a closed reentrant circuit. If the second pulse

Fig. 7. Peri-event rasters and histogram showing a caudate nucleus neuron's activity before and after the onset of the "go" signal indicated by the upgoing arrow. In the rasters each dot represents a neuronal discharge and each row represents a trial. Summing the column in the raster produces the histogram. As can be seen with no stimulation, 100 pps DBS and to a lesser degree 50 pps DBS, there is an increase in neuronal discharge following the onset of the "go" signal. This dynamic modulation is lost with the 130 pps DBS. The post-stimulus histograms show the change in neuronal discharge probability following each stimulation pulse. The different lengths of data represent the different inter-stimulus intervals. As can be seen there is very little difference in the early and intermediate responses to the stimulation pulse with the different DBS frequencies. Further, DBS drives the neuronal activity even when the peri-event rasters and histograms demonstrate no modulation of neuronal activity with the behavior during stimulation at 130 pps (unpublished observations).

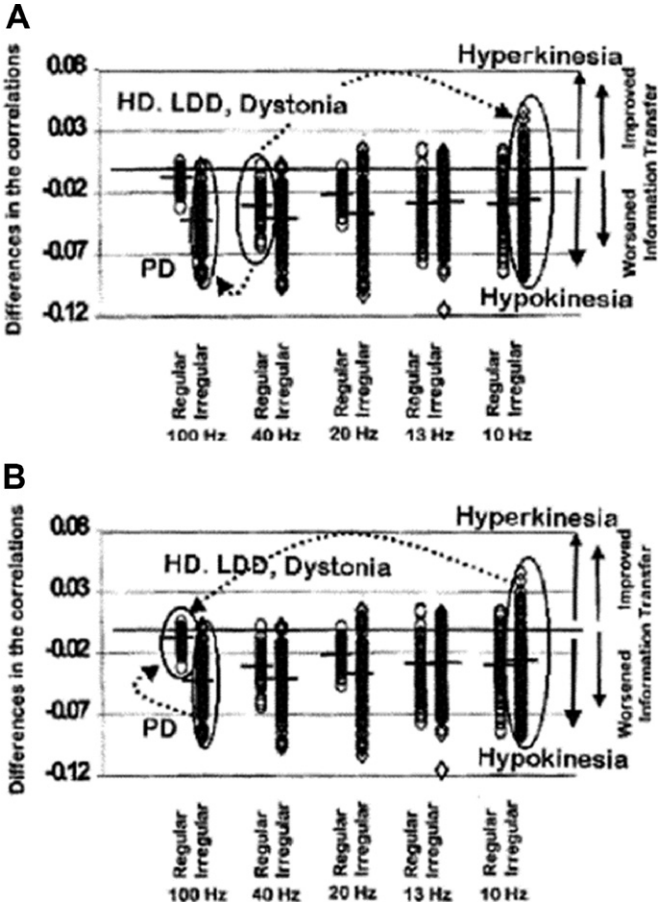


Fig. 9. Schematic representation of the misinformation/stochastic resonance theory of pathophysiology. The top graph represents information loss or gain from the computational modeling described in Fig. 6. The graphs represent repetitive iterations of information transfer between two neurons (X and Z in Fig. 8) affected by input from a third neuron (Y in Fig. 8). The activity of the third neuron varied in its regularity and frequency. As can be seen, there is considerable information loss (in neuron Z in Fig. 6) with irregular and with low frequency activity (in neuron Y in Fig. 8). With both Parkinson's disease (PD), Huntington's disease (HD), levodopa-induced dyskinesia (LDD) and in dystonia, the pattern of GPi activity becomes irregular. This is analogous to the activity in neuron Y (Fig. 8) being 40 Hz and regular becoming 100 Hz and irregular in PD. GPi activity in HD, LLD, and dystonia becomes lower frequency and irregular (Papa et al., 1999; Vitek et al., 1999) analogous to neuron Y going from 40 Hz regular to 10 Hz irregular. The consequence is information loss resulting in poor motor function. In addition, at 10 Hz irregular activities, there are episodes of abnormal information gain and this could be analogous to the involuntary movement of HD, LLD and dystonia. The bottom panel represents what might occur with high frequency and regular DBS. There is a change in activity in neuron Y (Fig. 8) to high frequency and regular. This results in less information loss and abnormal information gain that might normalize motor function. From (Montgomery, 2003) modified from (Montgomery and Baker, 2000).

is delivered at the same time reentrant activity within the closed loop returns to the initiating sight, there will be an increase in neuronal excitability indicated by an increased probability of a neuronal discharge. Fig. 12 shows an example of the results. Each row is associated with a different inter-stimulus interval. The horizontal axis indicates the time of the resonance effect following the second stimulus pulse. A significant increase in the probability of a neuronal discharge is color-coded reflecting z score changes from the pre-stimulation baseline.

As can be seen in Fig. 12, a resonance effect can be seen at 3.8 ms following the second pulse when the first pulse occurred 1 ms before. This effect reflects post-synaptic summation of the paired pulse. Similarly, there is a resonance effect with a 2 ms inter-stimulus interval but not at 3 ms but again at longer inter-stimulus intervals. The absence of a resonance effect at 3 ms may reflect the refractory period.

The possibility that periodic mechanisms intrinsic to the membrane following an action potential resulted in the resonance effect was evaluated by examining the auto-correlogram. The refractory period and post-refractory period increased excitability were demonstrated. For 71%, no changes in the membrane excitability were found at time periods associated with the inter-stimulus intervals that produced resonance effects. The reasonable conclusion is that these resonance effects associated with longer inter-stimulus intervals were not due to intrinsic membrane properties. Also, examination of Fig. 12 shows the resonance effect with 1 ms inter-stimulus interval at 3.8 ms was also seen at 7.6 and 15.2 ms suggest harmonics of a reentrant oscillator. Multiple resonance frequencies were found for all 118 neurons recorded in the BG-Th-Ctx system.

These results demonstrate clearly that the effects of a single DBS pulse are magnified when a second pulse is delivered after a specific an appropriate time delay in our paired-pulse stimulation studies. Further, not just any second stimulation pulse is sufficient. Consequently, it is clear that the effects of the first pulse are interacting with the effects of the second pulse. Also, the effects of the first pulse must recur at specific time intervals and not just persisting after the first pulse. Mere persistence would not explain the absence of response amplification at shorter time inter-stimulus intervals compared to the longer time intervals associated with amplification. Indeed, we demonstrated recurrent increases in neuronal excitability are several time periods following DBS pulses consistent with that demonstrated by Bergman and colleagues (Bar-Gad et al., 2004). Consequently, it is reasonable to conclude that the responses to the first stimulation pulse are periodic. Similarly, it is reasonable to infer that the effects of the second pulse also would be periodic. Therefore, the amplification of the periodic recurring activity generated by the first pulse by the possible periodic activity generated by the second pulse is consistent with standard definitions of resonance in physics.

While not proof of reentrant oscillators, these findings are consistent with reentrant oscillators. Further, resonance at short inter-stimulus intervals is consistent with high frequency reentrant oscillations and that multiple oscillators of different frequencies may coexist within a

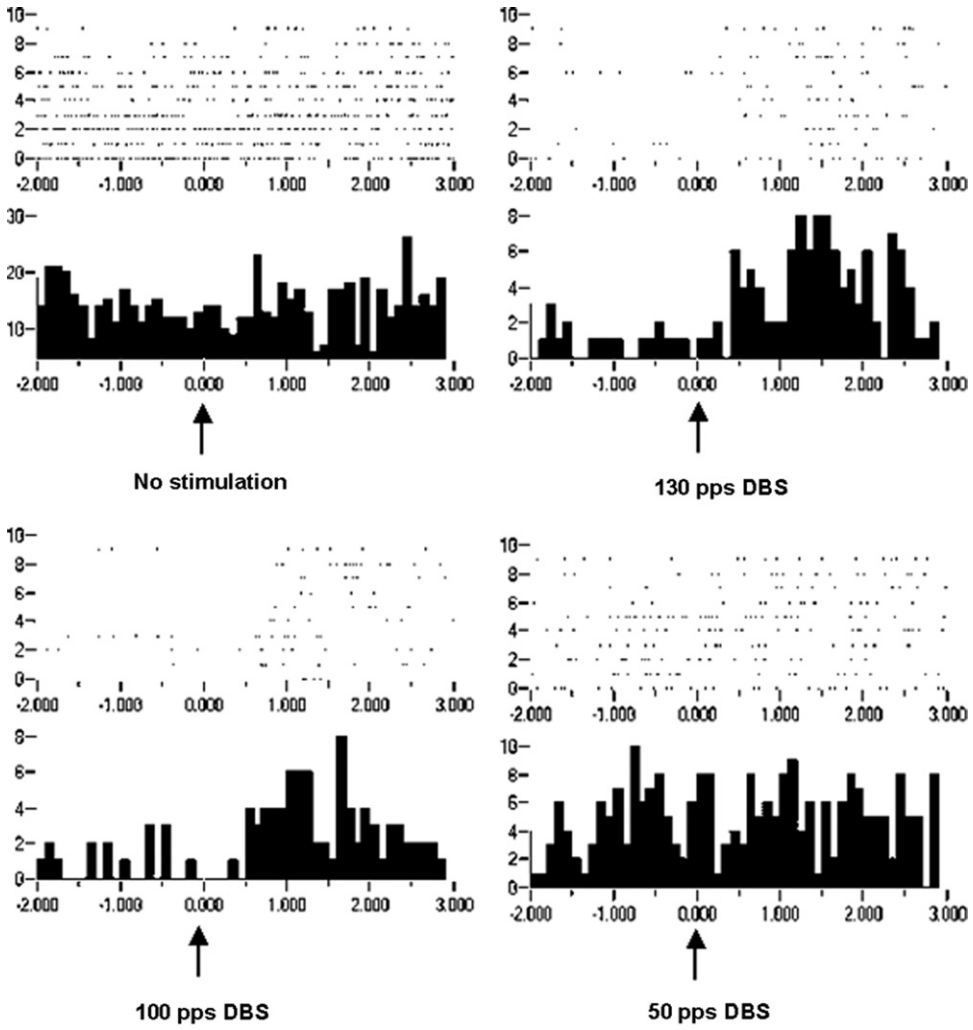


Fig. 10. Peri-event rasters and histograms for a neuron recorded in the Pt of a non-human primate. There is no meaningful modulation of neuronal activity with behavior (appearance of the "go" signal at time zero is indicated by the up-arrow) under the no stimulation condition. However, with 130 pps and to a lesser extent with 100 pps DBS, there is a consistent modulation, suggesting that the DBS has enlisted the neuron into being meaningfully related to the behavior. This would be consistent with (but not proof of) a resonance effect as described in the text (Gale, 2004). Note that the baseline activity before the "go" signal is reduced.

neuron. There is independent corroboration that neuronal spike trains demonstrate multiple and high frequency oscillators simultaneously (Montgomery, 2004b). A variation of the Schuster periodogram (Schuster, 1905) was used to detect periodic activity in the neuronal spike train. This method was applied microelectrode recordings from neurons in the BG-Th-Ctx system. Changes in frequency content over time were assessed by applying the periodogram to 2 s windows that are moved through the neuronal spike trains at 0.2 s steps. An example is shown in Fig. 13. As can be seen, there are multiple and high frequency oscillatory activity in the neuronal spike train simultaneously. Twenty-four neurons were recorded in GPe, 15 in GPi, 16 in Pt, 49 in sensory cortex, 9 in STN, and 25 in motor cortex (Gale et al., 2004). The average frequency was for each structure ranged from 135 to 140 Hz. It may not be coincidental that these frequencies are similar to the average therapeutic DBS frequencies (Deep Brain Stimulation in Parkinson's Disease Group, 2001).

The question arises, how such high and multiple reentrant oscillations are possible. This is not explained by the currently accepted theory of the BG-Th-Ctx as a hierarchical and sequential system (Albin et al., 1989, DeLong, 1990). Instead, the anatomical architecture of the BG-Th-Ctx system can be reconsidered as a set of nested non-linear reentrant loops. The physiological dynamics of such a system are very different. Fortunately, past mathematical modeling of such systems anticipated the physiological properties of biological systems such as a nested reentrant BG-Th-Ctx system. Hoppensteadt and Izhikevic (1997) demonstrated mathematically that such systems are capable of sustaining multiple frequencies simultaneously, a phenomena this author refers to as multi-stability after multi-stable vibrators in engineering terms.

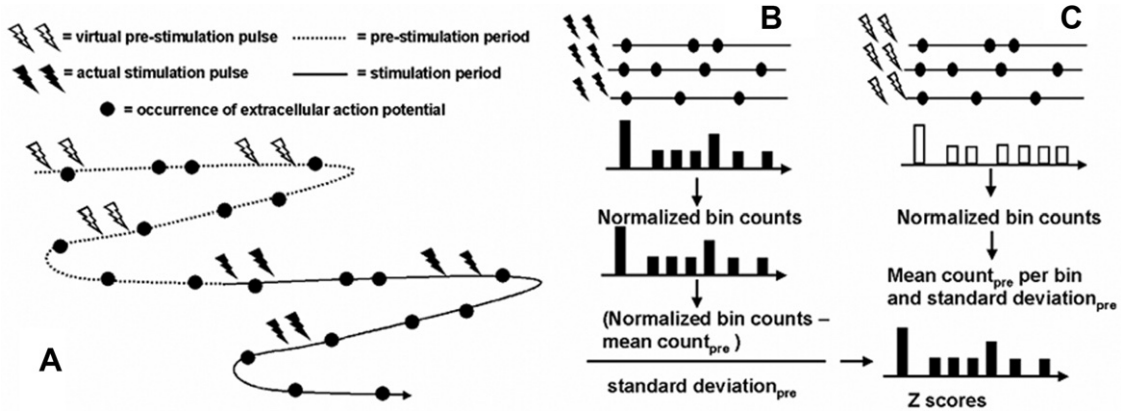


Fig. 11. Schematic representation of the analysis methods for detecting a resonance effect for paired-pulse stimulation. A set of virtual stimulus pulse pairs were created during the pre-stimulation period by translating the timing of the actual stimulation pulse pairs into the pre-stimulation period (A). Post-stimulus rasters and histograms were constructed indexed to the second pulse of the actual (B) and virtual (C) stimulation pulses. The rasters were collapsed across rows into the time bins (0.4 ms) of the histograms result in counts of extracellular action potentials. This was normalized by dividing by the number of sets of paired pulse stimuli resulting in probabilities of neuronal discharge in each time interval following the second of the stimulus pair. The mean probabilities per bin and the standard deviation were calculated for the virtual stimulation histograms (C). The mean was then subtracted from each time bin probability during the actual stimulation and divided by the standard deviation resulting in a z-score (B), modified from Montgomery (2004b).

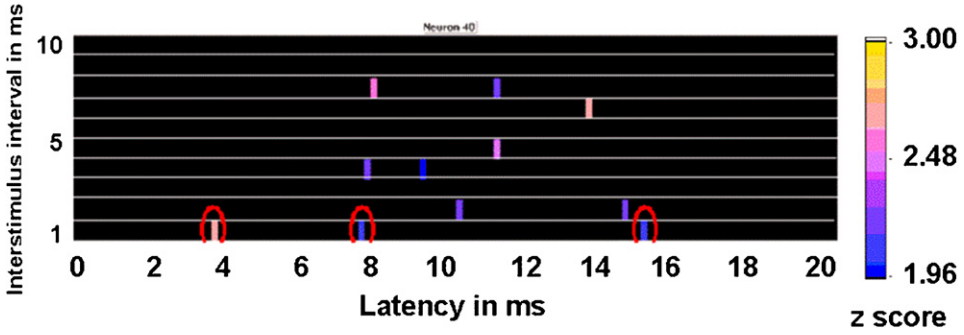


Fig. 12. Results from the paired-pulse experiments for a neuron recorded in the motor cortex of a non-human primate. Each row represents the changes in the probability of a neuronal discharge from baseline. Colored bars represent any change that has a z-score >1.96 compared to baseline. Each row corresponds to paired-pulse stimulation with interstimulus intervals ranging from 1 to 10 ms in 1-ms intervals. The horizontal axis represents the latency of the resonance effect after the test pulse (Montgomery, 2004b).

A new theory of basal ganglia function as part of a BG-Th-Ctx system and its supporting evidence has been reviewed by Montgomery (2004b).

Other investigators have discussed the importance of oscillators to basal ganglia function and pathophysiology (Amirnovin et al., 2004; Bergman et al., 1994; Bevan et al., 2002; Brown, 1997, Brown et al., 2001a,b; Devos et al., 2004; Hurtado et al., 1999; Hutchison et al., 2004; Karmon and Bergman 1993; Levy et al., 2000, 2002; Liu et al., 2002; McAuley et al., 2001; Meissner et al., 2005; Mochizuki et al., 1999; Nagasaki et al., 1978; Nakamura et al., 1978; Nini et al., 1995; Plenz and Kitai 1999,; Ruskin et al., 1999; Silberstein et al., 2003; Strafella et al., 1997; Terman et al., 2002; Titcombe et al., 2000; Williams et al., 2002). However, the large majority addresses oscillators at much lower frequencies than those described here, typically less than 70 Hz. The frequency is important as this relates to the bandwidth of the information that can be processed by these oscillators (Salinas et al., 2000). These studies do not address the neuronal mechanisms involved and provide only a modest explanation of how these oscillators may be involved in normal physiological or pathophysiological mechanisms and often these are discussed in terms of single oscillators rather than a network of multiple oscillators at many different and high frequencies (Gale and Montgomery, 2003; Gale et al., 2004; Montgomery, 2004b).

6. Implications of DBS for Theories of Physiology and Pathophysiology

It is safe to say that as yet it is not known how DBS exerts its therapeutic effect. However, DBS research as reduced the probability of some early notions such as inhibition of the stimulated target. Further, there are now a number of hypotheses that can compete and provide direction of future research. However, DBS research at the

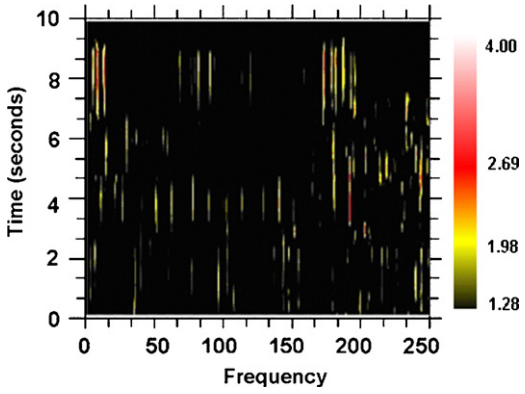


Fig. 13. Spectrogram showing the appearance and disappearance of significant frequencies in the discharge of a neuron recorded in the globus pallidus externa in a non-human primate. The circular statistics method is applied repeatedly over 10 s (vertical axis). The circular statistical method is applied to 2 s windows, which are then moved through time at 0.2-s increments. The circular statistics method is applied for periods (the inverse of the frequency) corresponding to frequencies from 1 to 250 Hz (horizontal axis). As can be seen, at every instant of time, multiple frequencies are represented in the neuronal spike train, from (Gale, 2004).

neuronal level has been successful because it has forced reconsideration of how the basal ganglia functions normally and in disease.

The demonstration that therapeutically effect DBS drives the output of the GPi well above abnormally high levels thought to cause parkinsonism, referred to as the Rate Hypothesis, clearly demonstrates the failure of the Rate Hypothesis, although there was considerable evidence nearly, 20 years ago counter to the GPi Rate Hypothesis (Montgomery et al., 1986). And if the GPi Rate Hypothesis is no longer tenable, what does this say about the physiological theory that provided the context for the GPi Rate Hypothesis? That theory can best be described as a sequence one-dimensional push pulls system where excitations and inhibitions are propagated in a serial and hierarchical manner (Salinas et al., 2000). Such dynamics reflect a process of thinking where the physiology is extrapolated from the anatomy. This approach, referred to as the Macro-neuron approach where single neurons are conceptually substituted for entire structures and the dynamics inferred from how a single neuronal in such an anatomical arrangement might respond. It is clear now that such a conceptualization is profoundly misleading.

Again DBS research has demonstrated the limitations of macro-neuron approach to physiological theory making. A study of the effects of VL neurons in a human with GPi DBS described above illustrates this point. This study confirmed similar studies of VL neurons in non-human primates with GPi stimulation in which the majority of VL neurons had a reduction in activity with GPi stimulation (Anderson et al., 2003). In the human study, every neuron demonstrated inhibition with a latency of approximately 2.5 ms and lasting 2.5 ms (Montgomery, 2006). However, like the non-human primate study, a significant number of VL neurons demonstrated an increase in VL neuronal activity. In the non-human primate 16% showed an increase in the average discharge frequency while in the human studies, 20% of the recorded neurons increased their average discharge frequency.

In the human study, 24% of the 25 VL neurons demonstrated a rebound increased neuronal discharge rate following the GPi induced inhibition (Fig. 3). This is not consistent with the current concepts of basal ganglia physiology and pathophysiology. The question arises as to how significant is the 24% that demonstrated post-inhibition rebound increased activity? This is a difficult question to answer, as this percentage does not include those neurons that had a subthreshold post-inhibition increased excitability. It is possible that during the course of behavior the increased motor cortex activity projecting to the VL could combined with the post-inhibitory rebound excitability consequent to GPi activity to actually increase VL activity. This may explain why increased neuronal activity with behavior is the dominant feature in motor cortex, VL (MacMillan et al., 2004), and GPi (Jaeger et al., 1995; Mink and Thach 1991) rather than the reciprocal changes the current anatomically driven macro-neuron derived theory of basal ganglia function would predict.

7. Future DBS research at the Neuronal Level

DBS research also illustrates the categorical logical error that has dominated current approaches to studying basal ganglia pathophysiology, particularly related to parkinsonism. A categorical logical error (Ryle, 2000) is where findings in one category or context are extrapolated to a different category or context. In this case, the error is extrapolating from changes in neuronal activities at rest in studies of diseases or models of disease to what may occur during behavior. The limited preliminary data described here (Fig. 10) clearly demonstrate changes in the dynamic modulation of neuronal activities in the presence of DBS that could not be anticipated by neuronal responses to DBS. Similarly, the lack of studies of parkinsonian pathophysiology at the neuronal level in animal models of the disease correlated with behavior is striking. The authors knows of only one research article (Doudet et al., 1990) and three abstracts (Mandir et al., 1989; Montgomery, 1993; Watts et al., 1989) that studied changes in the dynamic behaviorally related modulation of neuronal activity with induction of Parkinsonism with *n*-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP). These cases were studies of the motor cortex, Pt and supplementary motor areas (SMA) but again there was a striking discordance between changes in baseline neuronal activity and the changes in movement related dynamics.

With the remarkable advances in the molecular biology of movement disorders, such as increase understanding of neurotoxins or genetic mechanisms of cellular dysfunction, the question arises as to the need or priority of DBS and pathophysiological research at the neuronal level. While it

may be reasonably optimistic that the molecular biological researches will lead to prevention of disease or arrest in disease progression, it may be overly optimistic to believe that these approaches will lead to a cure in the foreseeable lifespan of those affected by movement disorders. To those present and future patients, there is an obligation to improve their disabilities and to optimize their function and independence.

The remarkable clinical benefits of DBS (Deep Brain Stimulation in Parkinson's Disease Group, 2001) and the failure of fetal dopamine cell transplant (Olanow et al., 2003) for Parkinson's disease clearly demonstrates the importance of understanding the neuronal mechanisms of disease. Fetal dopamine cell transplantation certainly was successful at replenishing the Pt with dopamine but this failed to provide significant clinical benefit. Indeed, the majority of patients developed involuntary movements and many of these patients required DBS surgery or pallidotomy to abolish the involuntary movements. These observations and the demonstration of DBS efficacy in the face of pharmacological treatment failure (Deep Brain Stimulation in Parkinson's Disease Group, 2001) clearly demonstrate that Parkinson's disease is not purely a dopamine deficient state. Rather it is a derangement of a complex dynamical state. Improvements in symptomatic therapies will require addressing these complex dynamical states.

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