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Basal ganglia activity patterns in parkinsonism and computational modeling of their downstream effects

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Abstract

The availability of suitable animal models and of the opportunity to record electrophysiologic data in movement disorder patients undergoing neurosurgical procedures has allowed researchers to investigate parkinsonism-related changes in neuronal firing patterns in the basal ganglia and associated areas of thalamus and cortex. These studies have shown that parkinsonism is associated with increased activity in the basal ganglia output nuclei, along with an increase in burst discharges, oscillatory firing, and synchronous firing patterns throughout the basal ganglia. Computational approaches have the potential to play an important role in the interpretation of these data. Such efforts can provide a formalized view of neuronal interactions in the network of connections between basal ganglia, thalamus and cortex, allow for the exploration of possible contributions of particular network components to parkinsonism, and potentially result in new conceptual frameworks and hypotheses that can be subjected to biological testing. It has proven very difficult, however, to integrate the wealth of the experimental findings into coherent models of the disease. In this review, we provide an overview of the abnormalities in neuronal activity that have been associated with parkinsonism. Subsequently, we discuss some particular efforts to model the pathophysiologic mechanisms that may link abnormal basal ganglia activity to the cardinal parkinsonian motor signs and may help explain the mechanisms underlying the therapeutic efficacy of deep brain stimulation for Parkinson's disease. We emphasize the logical structure of these computational studies, making clear the assumptions from which they proceed and the consequences and predictions that follow from these assumptions.

Keywords

Parkinson's disease; dopamine; striatum; globus pallidus; subthalamic nucleus; deep brain stimulation; burst; oscillation; synchrony

1. Motivation

There is little doubt that degeneration of the dopaminergic innervation of the basal ganglia (BG) is the essential pathologic defect that results in the motor signs of Parkinson's disease (PD), which include akinesia, bradykinesia, rigidity and tremor. A major advance toward

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understanding how this local loss of dopamine leads to the genesis of parkinsonian signs came with the discovery that abnormalities in the discharge of BG output neurons constitute a critical intermediate step in the pathophysiology of PD. However, wide gaps remain in our understanding. One serious impediment to further progress is the fundamental challenge of understanding how the firing patterns of large populations of neurons influence neuronal network function.

Computational models provide a way to formalize and quantify otherwise vague concepts of neuronal network function and how abnormalities in neuronal firing, like those observed in PD, may disrupt network function. One might argue that the only way to truly “understand” the pathophysiology of PD is to model it computationally.

In this review, we provide an overview of the abnormalities in neuronal activity that have been associated with PD and then discuss efforts to model some particular pathophysiologic mechanisms that may translate abnormal patterns of neuronal activity in the BG into the cardinal signs associated with that disorder, as well as how this process may be affected by deep brain stimulation (DBS).

2. Anatomy and pathology in parkinsonism

The BG are a group of heavily interconnected subcortical nuclei (Alexander *et al.*, 1990) (Fig. 1a). The striatum, the primary receptive nucleus of the BG, receives afferent projections from almost all areas of the neocortex, from specific nuclei of the thalamus, and from dopaminergic neurons of the substantia nigra compacta (SNc). The neocortical projections are organized into parallel anatomically-segregated pathways for skeletomotor, oculomotor, associative, and limbic regions of cortex and the striatum (Alexander *et al.*, 1990). A second important input pathway into the BG arises from pre-central cortical areas and terminates topographically in the subthalamic nucleus (STN).

The primary output projections from the BG are GABAergic efferents arising from neurons in the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). These efferents terminate in specific nuclei of the thalamus [the anterior portion of the VL nucleus (VL_a), the ventral anterior nucleus of the thalamus (VA) and intralaminar nuclei] (Yoshida *et al.*, 1972; DeVito & Anderson, 1982) and in midbrain nuclei such as the pedunculopontine nucleus (PPN) and superior colliculus. BG efferent neurons have high spontaneous discharge rates in neurologically-normal animals at rest [mean firing rates of 40–80 Hz (DeLong, 1971; Wichmann *et al.*, 1999; Starr *et al.*, 2005)], which are thought to produce a tonic inhibition of their targets in the thalamus and midbrain.

Similar to the organization of BG input, efferent projections from the BG show an anatomically-segregated functional organization such that distinct regions of the GPi and SNr project to skeletomotor-, oculomotor-, associative-, and limbic-related regions of the thalamus (Hoover & Strick, 1993; Middleton & Strick, 2000). Neurons that project to motor- and premotor-related regions of thalamus are located in the posterior GPi, whereas those projecting to prefrontal-related thalamic nuclei are located in the anterior dorsal GPi and the SNr.

Much of the intrinsic connectivity of the BG can be captured by the classic model that identifies “direct” and “indirect” pathways that connect the striatum to the BG output nuclei [GPi and SNr; Fig. 1a (Albin *et al.*, 1989; DeLong, 1990)]. The striatum contains two distinct populations of GABAergic projection neurons (termed “medium spiny neurons,” MSNs), those that project directly to the BG output nuclei and those that project only indirectly (Albin *et al.*, 1989; Gerfen *et al.*, 1990). Indirect-type MSNs project to an intermediate nucleus, the external globus pallidus (GPe), which in turn sends GABAergic

projections to the output nuclei and to STN. The STN sends glutamatergic efferents to the GPi and the GPe. As will be seen below, the direct/indirect pathway model provides a useful framework for understanding initial stages of the pathophysiology of PD.

Some BG connectivity is not included in the standard direct/indirect pathway model. For example, the cortico-subthalamic pathway provides what has been described as a “hyper-direct” pathway by which excitatory cortical input can influence the activity of both segments of the globus pallidus (Nambu *et al.*, 2004). Also, a sub-population of GPe neurons project “back” to the striatum where they differentially innervate a specific type of striatal interneuron (Parent & Parent, 2002). Recent work has also reported disynaptic interactions between the BG and the cerebellum. The deep cerebellar nuclei project to the striatum via a cerebello-thalamo-striatal pathway (Hoshi *et al.*, 2005) and the STN projects to cerebellar cortex via pre-cerebellar nuclei of the brainstem (Bostan *et al.*, 2010). The functional significance of these newly-discovered pathways remains unclear.

The cardinal motor signs of PD arise from degeneration of the dopaminergic neurons in the SNc and of their extensive axonal arborizations in the striatum and other BG nuclei (Fig. 1b). It is important to recognize, however, that PD is a complex disease associated with progressive degeneration of neurons from many sites in the central and peripheral nervous systems (Ruberg *et al.*, 1986; Scatton *et al.*, 1986; Zweig *et al.*, 1993; Braak & Braak, 2000; Henderson *et al.*, 2000a; Bohnen & Albin, 2011). Degeneration of the dopaminergic neurons of the SNc is one feature of that complex pathology. Some of the other, non-dopaminergic, features of the disease will be mentioned below. Despite the complexity of the disease, the clinical importance of the association between the cardinal motor signs of PD and the loss of dopamine is indicated by the spectacular therapeutic efficacy of dopamine replacement therapies (Hornykiewicz & Kish, 1987).

3. Activity patterns associated with PD

Loss of dopaminergic innervation is known to induce a variety of abnormalities in cellular excitability, synaptic plasticity, and even cell morphology in the striatum (Ingham *et al.*, 1989; Day *et al.*, 2006; Shen *et al.*, 2008; Gerfen & Surmeier, 2011) and, though investigated to a lesser extent, in other BG nuclei as well (Rommelfanger & Wichmann, 2010). One (potentially indirect network-mediated) consequence of these diverse cellular changes is the appearance of abnormalities in neuronal discharge in BG nuclei and in connected regions of the thalamus and cortex (figure 2). Abnormal discharge exiting the BG via projections from the GPi constitutes an essential intermediate step in the genesis of parkinsonian motor signs. There is little doubt that this is the case given the remarkable antiparkinsonian effects of lesions of the GPi (pallidotomy) in parkinsonian patients (Laitinen, 1995; Lozano *et al.*, 1995; Vitek *et al.*, 2003) and GPi inactivation in animal models of parkinsonism (Brotchie *et al.*, 1991; Lieberman *et al.*, 1999; Baron *et al.*, 2002).

a. Rate changes

An inherent component of the direct/indirect pathway model, as originally stated, was the prediction that abnormalities in mean discharge rate play an essential role in the pathophysiology of PD. According to the model, loss of striatal dopamine causes reduced discharge rates in direct pathway MSNs and increased discharge in indirect pathway MSNs. Both of these changes promote increased spontaneous discharge in GPi (Figure 1b and Albin *et al.*, 1989; DeLong, 1990). Abnormally-elevated discharge of inhibitory GPi neurons was proposed to interfere with the normal movement-related activation of GPi-recipient thalamus and thereby generate the hypokinetic features of PD. The rate model predicts that resting discharge rates should be elevated in STN and GPi and depressed in GPe, GPi-recipient thalamus and in connected regions of the motor cortices.

Predictions of the rate model have been supported by single unit recording studies in monkeys rendered parkinsonian by treatment with the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). These studies found elevated firing rates in the GPi and STN and depressed rates in GPe, thalamus, and motor cortex (Miller & DeLong, 1988; Filion & Tremblay, 1991; Bergman *et al.*, 1994; Schneider & Rothblat, 1996; Elder & Vitek, 2001; Pasquereau & Turner, 2010). Studies using indirect markers of neuronal activity (levels of 2-deoxyglucose uptake, cytochrome oxidase or immediate-early gene expression) have also reported changes in the BG, thalamus and motor cortices consistent with the rate model (Crossman *et al.*, 1985; Vila *et al.*, 1997; Steiner & Kitai, 2000; 2001; Orioux *et al.*, 2002; Emborg *et al.*, 2007; Rolland *et al.*, 2007). Moreover, single unit recording studies in patients undergoing surgical therapies have yielded increased firing rates in the parkinsonian GPi and reduced rates in thalamus as compared with rates in those structures in other neurologic disorders (Hutchison *et al.*, 1994; Molnar *et al.*, 2005; Chen *et al.*, 2010) or in neurologically normal monkeys (Starr *et al.*, 2008). Further support for the rate model came from the observation that parkinsonian signs are alleviated by manipulations that reduce STN discharge rates [i.e., permanent lesion (Bergman *et al.*, 1990; Gill & Heywood, 1997; Alvarez *et al.*, 2005), transient inactivation (Wichmann *et al.*, 1994; Levy *et al.*, 2001b; Baron *et al.*, 2002), or genetic manipulation (Luo *et al.*, 2002; Emborg *et al.*, 2007; Lewitt *et al.*, 2011)].

Despite those results, it is now recognized that aspects of the rate model are not tenable. Many studies have reported that firing rates in the pallidum, STN, thalamus, or cortex do not change in the way the rate model would predict with the induction of parkinsonism. Individual animals may be severely parkinsonian, but show no significant increase in STN or GPi discharge rates (Wichmann *et al.*, 1999; Raz *et al.*, 2001; Rivlin-Etzion *et al.*, 2008) or decrease in thalamic or motor cortical activity (Doudet *et al.*, 1990; Watts & Mandir, 1992; Goldberg *et al.*, 2002; Pessiglione *et al.*, 2005; Rivlin-Etzion *et al.*, 2008). In addition, interventions such as DBS that yield significant therapeutic benefit can be associated with no net change in GPi firing rates (McCairn & Turner, 2009), or even increased rates (Anderson *et al.*, 2003; Hashimoto *et al.*, 2003; Hahn *et al.*, 2008). Conversely, manipulations that the rate model predicts should induce parkinsonism (e.g., lesions of GPe, see Soares *et al.*, 2004) do not result in the predicted effect.

Considering the mass of evidence in conflict with the classic rate model, it now seems clear that abnormalities in neuronal discharge pattern, beyond firing rate alone, play central roles in the genesis of parkinsonian signs. Taking a more nuanced perspective, however, it is still possible that abnormalities in discharge rate are important at specific points in the pathophysiologic process. Consistent with that idea, a recent study confirmed the predictions of the rate model for discharge rates of direct and indirect pathway MSNs (Kravitz *et al.*, 2010). Using optogenetic techniques, Kravitz *et al.* demonstrated that inhibition of direct pathway MSNs or increased activation of indirect pathway MSNs can induce parkinsonian signs. These results suggest that abnormalities in neuronal discharge rate and discharge pattern interact and possibly reinforce each other at different steps in the pathophysiologic chain. Such a mechanism could explain the continued accumulation of evidence for abnormal discharge rates at particular stages of the BG-thalamocortical (TC) loop circuit (Orioux *et al.*, 2002; Molnar *et al.*, 2005; Rolland *et al.*, 2007; Chen *et al.*, 2010; Pasquereau & Turner, 2010) despite the equally compelling evidence in conflict with a classic “monolithic” version of the rate model.

b. Burst discharges

Neurons in the GP and STN of parkinsonian animals frequently emit action potentials in bursts (short epochs of markedly elevated firing rate). Significant increases in the prevalence of burst firing have been reported for neurons in the GPi, GPe, and STN in neurotoxin

models of PD (Miller & DeLong, 1988; Fillion & Tremblay, 1991; Bergman *et al.*, 1994; Wichmann & Soares, 2006). Burst discharges are also a common feature of neuronal activity sampled from the GPi and STN of PD patients undergoing surgical therapies (Hutchison *et al.*, 1994; Magnin *et al.*, 2000). The increase in burst discharge appears early during the induction of experimental parkinsonism, roughly paralleling the time course of changes in discharge rate and metabolic activity (Ni *et al.*, 2000; Vila *et al.*, 2000; Breit *et al.*, 2007).

The burst discharges of the parkinsonian BG are often described as “oscillatory-” or “rhythmic-bursting,” thereby implying that bursts and oscillatory modulations in firing rate (see below) are essentially two facets of one underlying phenomenon (Raz *et al.*, 2001; Rivlin-Etzion *et al.*, 2008). Several observations suggest, however, that bursts and rhythmic modulations in firing rate may be independent phenomena (Kaneoke & Vitek, 1996). The prevalence of bursts and oscillatory firing have been found to vary independently in GPi neurons sampled from PD patients undergoing DBS implantation surgery (Wichmann & Soares, 2006; Chan *et al.*, 2011). Furthermore, therapeutic interventions may affect one measure (e.g., rhythmic firing) without changing the other (e.g., burst firing) (Levy *et al.*, 2001a; Garcia *et al.*, 2003; Heimer *et al.*, 2006; Hahn *et al.*, 2008; McCairn & Turner, 2009; Rosin *et al.*, 2011). Based on these observations, we consider bursts and oscillations separately here.

Increased burst firing has also been described for neurons in GPi-recipient regions of thalamus (Raeva *et al.*, 1999; Elder & Vitek, 2001; Pessiglione *et al.*, 2005), and in the motor cortices (Goldberg *et al.*, 2002; Pasquereau & Turner, 2011; Rosin *et al.*, 2011) in parkinsonism. It is important to note, however, that the bursts reported for thalamic and cortical activity have markedly different durations and timing than the bursts reported for neurons in the parkinsonian GP or STN. The difference in burst metrics may be explained by the fact that GPi-to-thalamic communication is mediated via GABAergic inhibitory synapses; bursts in GPi activity cannot generate bursts directly in thalamic and cortical activity. This nonlinearity at the GPi-to-thalamic synapse is a central feature in computational models discussed below. Whether thalamic and cortical bursts have metrics consistent with a post-inhibitory rebound mechanism is unknown at present.

A potentially confounding factor to be addressed in future studies is the possibility that previous observations of increased burst discharge in parkinsonism, particularly in thalamus and cortex, may be attributed to reduced levels of arousal and attentiveness in parkinsonian animals. A marked increase in burst discharges throughout thalamus and cortex is a well-established feature of reduced arousal and wakefulness (Steriade & Llinas, 1988) and reduced arousal and attentiveness are common in parkinsonian subjects (Rye *et al.*, 2000; Gatev & Wichmann, 2003; Barraud *et al.*, 2009).

c. Oscillatory firing patterns

Regularly recurring fluctuations in firing have been documented in the STN, GPi, GPe, and tonically active striatal interneurons (corresponding to cholinergic interneurons) in MPTP-treated monkeys (Bergman *et al.*, 1994; Nini *et al.*, 1995; Raz *et al.*, 1996) and in the STN and GPi of patients with PD undergoing electrophysiological recordings as part of neurosurgical procedures (Levy *et al.*, 2000; Levy *et al.*, 2002a; Levy *et al.*, 2002b). Most likely, oscillatory activity patterns arise as network phenomena, an aspect of BG activity that has been extensively studied with network simulations (see below). For instance, there is experimental support that oscillations can arise in the GPe-STN network, through interactions by which excitatory output from the STN leads to a burst of GPe spiking, which, in turn, leads first to hyperpolarization and then rebound bursting in the STN, resulting in renewed GPe bursting activity (Plenz & Kitai, 1999; Holgado *et al.*, 2010). Other mechanisms, for instance, STN driving by oscillatory cortico-subthalamic inputs, may also

lead to oscillatory bursting in the STN and related nuclei (Magill *et al.*, 2001; Magill *et al.*, 2004a; Magill *et al.*, 2004b).

Oscillatory activities in the BG-TC network of connections are also frequently studied in local field potential signals (LFPs). LFPs reflect synchronous membrane potential fluctuations of groups of neurons. The amplitude of these potentials is strongly dependent on the spatial arrangement of the electrically-excitabile tissue elements in the recorded area. The study of LFP recordings became very popular after the discovery that electrodes implanted in the BG of movement disorder patients for DBS therapy can be used as LFP recording devices. Analysis of oscillations in LFP records from such electrodes has revealed the occurrence of oscillatory activity in the beta frequency range (approximately 10–35Hz) throughout the extrastriatal BG (specifically in the STN), which can be suppressed by dopaminergic replacement therapies (Brown *et al.*, 2001; Levy *et al.*, 2002a; Williams *et al.*, 2002; Priori *et al.*, 2004; Kuhn *et al.*, 2009) or DBS therapy (Kuhn *et al.*, 2008; Bronte-Stewart *et al.*, 2009). At least in the STN of parkinsonian patients, single cell oscillations and beta-band LFP oscillations are related to one another (Kuhn *et al.*, 2005; Weinberger *et al.*, 2006). It is thought that LFP oscillations reflect dopamine-dependent oscillatory phenomena involving the entire BG–TC network of connections (Brown & Williams, 2005; Silberstein *et al.*, 2005; Hammond *et al.*, 2007). This conjecture is supported by evidence that beta oscillations in the LFP signals recorded in STN and GPi are coherent with cortical oscillatory electroencephalographic activity (Brown *et al.*, 2001; Marsden *et al.*, 2001; Cassidy *et al.*, 2002; Williams *et al.*, 2002; Fogelson *et al.*, 2005). In parallel with the presence of beta-band oscillatory activities, gamma-band oscillatory activities (frequencies > 35Hz) are found to be less prominent in the BG and cortex of parkinsonian patients and in animal models of the disease (Wang *et al.*, 1999; Brown, 2003; Lalo *et al.*, 2008).

Interestingly, while oscillatory activities are easily identified in the BG of parkinsonian patients and animal models, they are less clear in single-cell recordings from VLa and VA thalamic nuclei (but see Guehl *et al.*, 2003; Pessiglione *et al.*, 2005), although reduced gamma-band activation has been shown for thalamic LFP recordings from parkinsonian patients (Kempf *et al.*, 2009). Oscillatory activity is also less prominent in single cell recordings in primary motor cortex (Goldberg *et al.*, 2002; Pasquereau & Turner, 2011). A nonlinear transformation of activity in TC circuits may prevent BG oscillatory activity from directly inducing similar oscillatory activities at the single-cell level in cortex. However, the importance of cortical oscillatory activity continues to be a matter of debate. Interestingly, a recent study has shown that electrical stimulation of GPi with short trains of stimuli that were triggered by oscillatory single-cell activity in the primary motor cortex had strong antiparkinsonian effects (Rosin *et al.*, 2011).

d. Synchronization

There is rarely synchrony between the spontaneous discharges of different neurons in the BG of neurologically-normal subjects, supporting the general concept that the BG function as a series of parallel, largely independent modules (see above). This independence changes significantly in PD: neurons that are close to each other within areas located throughout the BG, the BG-receiving areas of the thalamus, and the cortex start to fire in synchrony (Bergman *et al.*, 1994; Goldberg *et al.*, 2002; Heimer *et al.*, 2002; Goldberg *et al.*, 2004; Rivlin-Etzion *et al.*, 2006; Hammond *et al.*, 2007). Studies of correlation patterns in human patients with PD and in non-human primates with parkinsonism have demonstrated that systemic treatment with dopamine receptor agonists acts to lower the level of abnormal synchronization in the firing of BG neurons (Levy *et al.*, 2001a; Heimer *et al.*, 2006), suggesting that the segregation of neuronal activity in the BG is, at least in part, actively maintained through the presence of dopamine.

Synchronous firing is often associated with oscillatory discharges. Such oscillatory synchrony is not only found within but also across the BG nuclei. For instance, oscillatory activity is synchronized across the STN, GPi and cortex, and this synchrony is suppressed by the administration of levodopa (Brown, 2003; Gatev *et al.*, 2006; Hammond *et al.*, 2007). As is the case for oscillatory activities at the single cell level (see above), the synchronous firing of single neurons in the STN is coherent with concomitantly recorded beta-band LFP oscillations (Kuhn *et al.*, 2005; Weinberger *et al.*, 2006).

The loss of independence between neighboring trans-BG channels is also apparent in the increased tendency of BG neurons to widen their receptive fields under parkinsonian conditions (Bronfeld & Bar-Gad, 2011). Under normal circumstances, BG neurons are usually highly specific in terms of their responses to sensory inputs, such as proprioceptive inputs during joint rotation. A widening of these receptive fields was found in recordings of neuronal responses in the STN, GP and thalamus of MPTP-treated monkeys (e.g., Filion *et al.*, 1988; Pessiglione *et al.*, 2005). The altered sensory field size may, in part, be a functional correlate of the greater degree of synchronized activities within the BG, but it may also reflect altered convergence patterns of sensory processing in these structures. It is not known whether the size of receptive fields is modulated specifically by the level of dopamine in the BG.

e. Generation of abnormal firing patterns

For many years, the absence of striatal dopamine has been thought to be solely responsible for the abnormal BG discharge patterns in parkinsonian conditions. Clearly, dopamine loss is the most prominent parkinsonism-related biochemical change in the BG, and the loss of dopamine at striatal synapses is likely to strongly influence corticostriatal transmission, and, thus, to affect activity patterns along the direct and indirect pathways (see above). Detailed computational models of the resulting activity changes have been developed, as is discussed in more detail below.

However, the dogma that BG firing abnormalities are entirely due to striatal dopamine loss has been challenged by recent studies documenting a widespread pattern of additional changes in the brains of parkinsonian subjects, which may also influence activity patterns in the BG in parkinsonism. One of these recently recognized parkinsonism-associated changes is that dopamine is not only lost in the striatum, but throughout the extrastriatal BG, thalamus and frontal cortex, which, based on electrophysiological studies, may strongly (and directly) affect the activity of neurons in these areas (reviewed in Rommelfanger & Wichmann, 2010). Furthermore, PD in humans and experimental parkinsonism in animals is associated with the early loss of norepinephrinergic cells in the locus coeruleus and other catecholaminergic brain stem regions (Braak *et al.*, 2004; Masilamoni *et al.*, 2011). As mentioned above, PD and toxin-induced parkinsonism in animals is also associated with a variety of structural changes in the BG and associated areas, which may further affect firing patterns in the BG. For instance, it is known that synapses of corticostriatal projections and dendritic spines of striatal medium spiny neurons degenerate in PD (reviewed in Villalba & Smith, 2010; 2011), and similar changes may also occur at glutamatergic terminals of the cortico-subthalamic projection (Mathai *et al.*, 2011). Another recently documented change is the finding that the thalamic source neurons of the massive thalamostriatal projection system (located in the caudal intralaminar nuclei of the thalamus) degenerate in patients with advanced PD and in animal models of the disease (Freyaldenhoven *et al.*, 1997; Henderson *et al.*, 2000a; b; Ghorayeb *et al.*, 2002; Henderson *et al.*, 2005; Aymerich *et al.*, 2006; Villalba *et al.*, 2011).

f. The role of abnormal BG discharge in the expression of parkinsonism

The link(s) between specific changes in the discharge patterns of BG neurons and the behavioral manifestations of PD remain(s) tenuous. One approach to investigating this issue is to examine the temporal relationship between the development of parkinsonism and the occurrence of abnormal discharge patterns in the BG. Such studies have confirmed that the neuronal activity in STN and GPi is increased prior to the onset of motor symptoms (Bezard *et al.*, 1999). Furthermore, BG interventions such as lesions or DBS of GPi or STN dramatically and immediately improve parkinsonian signs, supporting a role of BG discharge abnormalities in the development of parkinsonism (Wichmann & DeLong, 2006).

A very large body of literature is devoted to an exploration of the role of oscillatory activity in movement, and the possible disturbing effects of enhanced beta-band oscillations in the BG-TC network of connections. In normal individuals, beta band oscillations are reduced immediately prior to and during voluntary movements in cortex (Pfurtscheller & Neuper, 1992; Toro *et al.*, 1994; Leocani *et al.*, 1997; Ohara *et al.*, 2000; Alegre *et al.*, 2002; Doyle *et al.*, 2005b) and putamen (Courtemanche *et al.*, 2003; Sochorukova & Rektor, 2003), concomitant with an increase in gamma-band activities. Movements are followed by a resurgence of beta-band oscillations, suggesting that beta-band activity may have movement-terminating or suppressing effects. In patients with implanted DBS electrodes, a similar general relationship between beta-band activity and movement was demonstrated for LFPs in the STN (Cassidy *et al.*, 2002; Williams *et al.*, 2003; Kuhn *et al.*, 2004; Doyle *et al.*, 2005a; Williams *et al.*, 2005; Kuhn *et al.*, 2006; Kempf *et al.*, 2007). It is thought that the increased 'anti-kinetic' oscillatory activity in the beta-band in the BG may interfere with movement initiation in parkinsonian patients (akinesia).

Evidence for a direct role of abnormal BG activities in parkinsonism also comes from studies involving electrical stimulation of the STN in monkeys. These experiments have shown that motoric impairments can be induced with stimulation patterns fashioned after those recorded in parkinsonian animals (Ma & Wichmann, 2004), that movement is slowed by stimulation at beta-band frequencies (Timmermann *et al.*, 2004; Chen *et al.*, 2007; Eusebio *et al.*, 2009), and that parkinsonism can be improved with oscillatory trains of stimuli timed to eliminate the beta-band activities in the BG (Rosin *et al.*, 2011).

In contrast to these studies, several animal studies have found that the neuronal activity changes (particularly oscillatory activities) appear only after the emergence of parkinsonism and, therefore, cannot be fully responsible for it (Leblois *et al.*, 2007). Likewise, in studies in rodents in which nigrostriatal dopaminergic transmission was blocked acutely with dopamine antagonists at doses that induce parkinsonism, oscillatory neuronal activities were not seen in the BG and cortex (Mallet *et al.*, 2008; Degos *et al.*, 2009), contrasting with the outcome of more chronic dopamine depletion strategies. Furthermore, despite the consistent finding of increased burst firing in the BG in parkinsonism, treatments with dopaminergic agents do not always reduce burst firing in the BG of parkinsonian animals or patients (compare Tseng *et al.*, 2000; Lee *et al.*, 2001; Levy *et al.*, 2001a). Local injections of dopamine D1-like receptor agonists into the primate GPi or SNr, or D5 receptor activation in the rodent STN, were also found to increase rather than decrease burst firing in these nuclei (Baufreton *et al.*, 2003; Kliem *et al.*, 2007). Additionally, therapeutic DBS of the GPi (McCairn & Turner, 2009; Rosin *et al.*, 2011) or STN (Hahn *et al.*, 2008) is not accompanied consistently by reductions in the prevalence of GPi burst discharges.

4. A perspective on computational modeling

Given the complexity of the brain, there is little hope of building a computational representation of even a limited brain area, much less of something like the BG, that is both

a complete model and of practical utility. Nonetheless, we claim that computational and mathematical methods (Dayan & Abbott, 2001; Izhikevich, 2007; Ermentrout & Terman, 2010) offer a means to explore and generate hypotheses and experimentally testable predictions about the BG in parkinsonism. As we have described in the earlier sections of this article, there are a variety of alterations that have been experimentally and clinically observed to occur in the BG in the parkinsonian condition. Many of these are changes in activity in various nuclei, including modulations of firing rates, of temporal patterns of firing, and of correlation patterns and response specificities. One natural direction for computational efforts is to explore the mechanisms underlying the emergence and properties of parkinsonian activity within model BG circuits.

It is possible that some or all of these changes actively contribute to motor impairment, or it may be that they are consequences of some other factors that cause the dysfunctions. To address this paradigmatic dichotomy, one alternative but reasonable approach is to pick a particular change in activity and ask, given that this change occurs, how could it lead to motor effects, and what would these effects be? While this is a reductionist step, it is potentially powerful in allowing for the examination of the logical consequences of a small set of initial assumptions (Silva, 2011). Indeed, we claim that this approach is essential to developing a complete understanding of parkinsonian pathophysiology, bridging from the loss of dopamine and other aspects of the onset of parkinsonism to the emergence of its motor (our focus here) and other signs, and to explaining the impact and efficacy of treatments for parkinsonian patients.

A variety of models and modeling frameworks that have been employed in the context of parkinsonism and DBS therapy have been reviewed elsewhere (Titcombe *et al.*, 2004; Modolo *et al.*, 2011). To constrain the scope of this article and match the emphasis in the literature, we will focus on modeling the link from alterations in BG activity to their possible downstream effects, along with the possible impact of STN DBS on this pathway. We first discuss a specific reduced model, with an emphasis on the underlying logic (assumptions, consequences, and predictions). Beyond this particular line of investigation, we subsequently review some complementary and alternative computational approaches to understanding the therapeutic effects of STN DBS, which also build from starting points based on certain aspects of parkinsonian activity.

5. A computational framework based on thalamic relay

a. Foundations for the framework

Taking this approach, consider the excessive bursting found in the parkinsonian BG. The dynamic mechanisms underlying the bursting are critical in terms of evaluating how possible therapeutic interventions might impact or target this phenomenon, and various mechanisms have been proposed and studied computationally (Terman *et al.*, 2002; Kubota & Rubin, 2011). First, however, to determine the possible pathological motor implications of excessive bursting, a natural starting point is to consider where it occurs and, crucially, what other brain areas receive inputs from the sites exhibiting excessive bursting. Two sites with prominent increases in bursting that project out of the BG are the STN and the GPi. The STN projects to the PPN, so one possibility is that the effects of STN bursting on PPN are critical to motor complications. However, there is significant loss of PPN neurons in parkinsonian conditions (Pahapill & Lozano, 2000). Thus, we again make a reductionist choice and ignore this pathway to focus on outputs of GPi. That is, we ask the specific question, how could excessive bursting in GPi translate into altered motor behavior? As reviewed above, GABAergic neurons of the “motor” GPi project to the anterior ventrolateral nucleus of thalamus (VL_a) (Yoshida *et al.*, 1972; DeVito & Anderson, 1982; Jones, 2007).

Therefore, to pursue this line of reasoning, the key issue is how excessive bursting in GPi impacts VLa thalamus.

In fact, how GPi output affects the spiking activity in VLa is poorly understood. In the normal brain, BG projections to the thalamus are not principal drivers of thalamic activity. Sensory-evoked responses typically begin earlier in VLa than in GPi (DeLong *et al.*, 1985; Vitek *et al.*, 1994), suggesting that thalamic responses are driven by an earlier-firing non-BG source. Also, transient inactivation of the GPi does not alter task-related activity in VLa, even when it increases resting firing rates (Inase *et al.*, 1996). Thus, in the normal brain, BG afferents appear to modulate thalamic activity that is driven by some other component (e.g., excitatory inputs from cortex) (Deniau & Chevalier, 1985; Inase *et al.*, 1996). Rubin and Terman introduced the idea of using computational models to study how bursty inhibition from GPi might affect the response of TC relay cells to this excitatory drive (Rubin & Terman, 2004). Reduced TC cell models had been developed previously, for example, for the study of sleep spindles and absence epilepsy (Golomb *et al.*, 1994; Destexhe *et al.*, 1998; Sohal & Huguenard, 2002). These models feature various currents, but their dynamics are dominated by standard sodium and potassium spiking currents as well as a low-threshold or T-type calcium current. This T-current can give rise to post-inhibitory rebound or anodal break bursting, in which a sustained hyperpolarizing input slowly de-inactivates the current, opening one set of ion gates, and the subsequent abrupt removal of hyperpolarization activates the current, opening another set of gates and yielding a burst of rapid spikes (Jahnsen & Llinas, 1984a; b). In fact, a standard sodium current can also give rise to a similar but less pronounced rebound effect, due to its own slow inactivation component. While the T-type current tends to be more inactivated in awake than sleep states, evidence suggests that TC cell bursting is a component of awake dynamics, such as responses to novel stimuli, in sensory-driven thalamic areas (Sherman, 2001; Sherman & Guillery, 2002) and therefore the T-current should be included in models for awake states as well.

b. The Rubin/Terman (RT) model

For the study of what happens when a TC cell receives a burst of inhibition from GPi, Rubin and Terman considered several different sets of computational components (Rubin & Terman, 2004). In their most complete simulations and analysis, they synaptically connected model STN and GPe cells developed previously (Terman *et al.*, 2002) together with GPi and TC cells to form a small network featuring indirect and direct pathway components, with GPi cells inhibiting TC cells. Guided by earlier work (Terman *et al.*, 2002), they developed an architecture for the BG components of the network that allowed it to be tuned to generate irregular, asynchronous activity or to be retuned to yield bursty, synchronous activity in the 3–8 Hz range. The retuning consisted of changes in just two parameters, the strengths of inhibition from striatum to GPe and within GPe, which have been observed to occur experimentally in parkinsonian conditions (Albin *et al.*, 1989; Stanford & Cooper, 1999; Ogura & Kita, 2000). The model TC cells received inhibitory inputs from GPi as well as a computationally generated excitatory input train of spikes that were either periodic or Poisson. The authors calculated an error index to quantify the fidelity of the TC cell relay of its excitatory input. A successful relay consisted of a single TC spike within a small time window after an excitatory signal. Any other response to an excitatory input was considered an error. Specifically, unsuccessful events could be misses, in which no TC spike occurred during that window, or bad responses, consisting of multiple spikes after a single stimulus that did not reflect the excitatory input characteristics. The error index was given by the ratio of errors to the total number of excitatory input spikes.

The authors found that the switch from irregular to bursty activity within the BG significantly compromised the fidelity of TC relay, as quantified by the error index. Importantly, during a burst of GPi activity, the resulting TC cell inhibitory synaptic

conductance grows and then saturates at a high level, since the GPi spike rate is high relative to the time constant of inhibitory conductance decay. At the end of the burst, the conductance decays, and it subsequently remains low, until the next burst begins. Based on this observation, it is possible to analyze the loss of relay fidelity in terms of bifurcation diagrams or in terms of a simplified model and its nullclines (Rubin & Terman, 2004). This analysis reveals that under parkinsonian conditions, the TC neuron passes through four phases of distinct relay capacity: baseline, corresponding to low inhibition and low T-current availability; compromised, corresponding to high inhibition and low T-current availability shortly after GPi burst onset; recovered, corresponding to high T-current availability during sustained inhibition; and excessive, corresponding to low inhibition yet high T-current availability shortly after GPi burst offset (see Figure 3 for schematic illustration).

Part of the power of this framework is that it also offers an explanation for how STN DBS could achieve therapeutic efficacy. Experiments have shown that high-frequency stimulation can boost activity in its targets or can at least elicit effects consistent with augmented synaptic outputs from stimulated sites (Paul *et al.*, 2000; Windels *et al.*, 2000; Jech *et al.*, 2001; Anderson *et al.*, 2003; Hashimoto *et al.*, 2003; Hershey *et al.*, 2003; Windels *et al.*, 2003; Garcia *et al.*, 2005). If STN DBS drives GPi neurons in a way that leads to high amplitude but effectively sustained inhibition from GPi to its thalamic targets, then the computational model shows a significant restoration of thalamic relay fidelity. This effect arises even if the net TC cell inhibitory conductance oscillates, as long as the oscillation is of sufficiently high frequency and small amplitude. Mechanistically, the sustained inhibition leads to a sustained T-current deinactivation. The resulting current availability provides an extra boost that allows the model TC neuron to respond reliably to excitatory input spikes through its standard sodium and potassium dynamics. A similar effect would be expected with GPi DBS, again assuming that it results in a regularization of inhibition to pallidal targets in thalamus.

These results offer the first mechanistic theory for the proposed conceptual idea that pathological temporal variations in spike timing in the parkinsonian BG, such as burstiness or rhythmicity, could be disruptive to brain function and that elimination of these firing patterns could be correspondingly beneficial (Montgomery & Baker, 2000; Vitek, 2002; Foffani *et al.*, 2003; Grill *et al.*, 2004; Garcia *et al.*, 2005; Meissner *et al.*, 2005; Foffani & Priori, 2006). It is important to recognize the assumptions underlying this theory: the theory assumes that net inhibitory inputs to neurons within VLa thalamus are bursty in parkinsonism and that faithful relay of excitatory inputs by VLa thalamus is important for some aspects of normal motor activation. The theory also makes strong predictions, namely that at least some parkinsonian states should feature significant bursting in VLa thalamus, that elimination of prominent bursting or rhythmicity in the total GPi inputs to most cells in VLa thalamus should improve some motor features, and that changes in time constants of inhibition, T-current inactivation, or in sodium current inactivation within VLa thalamus should alter parkinsonism. More subtly, the theory implicitly predicts that for non-parkinsonian animals in states under which at least some symptoms occur in parkinsonism (e.g., awake resting state for rest tremor, movement initiation for bradykinesia), GPi outputs should be sufficiently irregular and asynchronous that TC cells can respond faithfully to excitatory inputs. Finally, the explanation offered for the mechanism of therapeutic efficacy of STN or GPi DBS relies on the idea that DBS yields a regularization of the inhibition from GPi to VLa thalamus, although the actual level of inhibition that results is not important. A prediction that follows is that any form of DBS, or other therapeutic modalities that eliminate GPi output patterning without compromising other aspects of BG output should also yield therapeutic benefit.

c. A data-driven version of the RT model and some limitations

Testing the importance of VLa relay fidelity for motor outcomes has thus far been beyond the reach of experiments. There is experimental data, however, on parkinsonian activity patterns in GPi and VLa thalamus that is relevant to this theoretical framework. Most directly, experimentally recorded spike trains from single primate GPi neurons were collected under several conditions: normal; MPTP-induced parkinsonism; MPTP plus STN DBS without therapeutic benefit (sub-DBS); and MPTP plus therapeutically effective STN DBS (Hashimoto *et al.*, 2003). In work by Guo *et al.* (Guo *et al.*, 2008), a collection of these trains were used to computationally generate continuous conductance signals. Each signal was used as an inhibitory synaptic conductance in a computational TC cell model, subject to the same forms of excitatory input used in previous work (Rubin & Terman, 2004), and again, a relay error index was computed. The GPi signals from the normal condition led to low error index scores, while, following MPTP, GPi signals yielded a very significant increase in error index. Crucially, the error index scores during sub-therapeutic DBS were also significantly elevated relative to normal, while scores were returned to normal levels with therapeutic DBS. Thus, regardless of the dynamic mechanisms conspiring to generate GPi activity patterns in various conditions, and independent of whether DBS activates, shuts down, or otherwise alters firing (where it is applied or upstream or downstream from there), we can conclude that the GPi signals that are present in parkinsonian conditions can compromise TC relay fidelity, while the application of therapeutic, but not sub-therapeutic, DBS leads to signals that support highly reliable relay.

While these results are exciting, there are reasons for caution: First, GPi spike trains had to be converted to continuous synaptic conductances, and this step required assumptions about synaptic parameters and dynamics. Second, a single-compartment computational TC cell model was used, necessitating an additional set of choices about currents to include and parameter values to use. Third, data was only available from one GPi neuron at a time, so no information about the patterns of activity across GPi within an experimental condition was available. Fourth, the data used was limited to 38 5-second blocks of spikes from 11 cells. Fifth, the data was obtained from non-human primates, rather than human patients. A subsequent study, however, did include data from GPi recordings in human PD patients; when this data was used in TC simulations, relay was compromised, while a phenomenological representation of DBS restored relay when DBS frequency was sufficiently high and DBS amplitude was within a particular band (Meijer *et al.*, 2011). Sixth, the simulations did not incorporate any specific features of the architecture of synaptic connections, such as divergence or convergence, from GPi to thalamus. Finally, results from a number of empirical studies have brought into question the pathophysiologic importance of burst discharges in the GPi (see sections 3b and 3f, above) Follow-up studies that link additional experiments and simulations to move beyond these limitations could make an important contribution to our understanding of these effects.

Interestingly, several aspects of the data-driven computational results (Guo *et al.*, 2008) point to the importance of GPi bursting in determining relay outcomes. The fraction of time over which the data-driven GPi inhibitory input signals were elevated rose steadily from normal to MPTP to sub-DBS to DBS conditions, corresponding to a progression from irregular to bursty to high frequency, relatively sustained spiking. Supplying the same GPi signal to a heterogeneous population of model TC cells caused independent TC relay failures in normal and DBS cases, but the failures were synchronized across the TC population in MPTP and sub-DBS cases, pointing to the robustness of the effects of inhibitory bursts on the model TC neurons. Finally, averaging GPi signals that gave identical TC responses to an excitatory input (successful relay, failure to spike, or excessive response), aligned relative to each excitatory input (i.e., using the 20 ms of signal before each input and the 5 ms of signal after it), revealed significant differences across the three

response types. Average inhibitory conductance was relatively constant before successful responses but showed a pronounced rise before spike failures and decline before excessive responses (Figure 4). These results reflect the power of relatively rapid changes in inhibitory conductance, as would be associated with synchronized GPi bursting, to interfere with the straightforward relay of an excitatory input.

Thus, while these data-driven computational results circumvent the issue of burst generation mechanisms, they bring us back to the question of bursting in VLa thalamus. A small number of monkey studies have suggested that some bursting is present and may be reduced by DBS. Specifically, following MPTP injections, effective but not ineffective STN DBS regularized firing and reduced bursts in the pallidal receiving areas of motor thalamus (Xu *et al.*, 2008). Moreover, in monkeys in which bursting was observed in a small subset of downstream thalamic neurons, GPi DBS reduced the prevalence of this activity pattern and the number of spikes per burst when bursting remained (Anderson *et al.*, 2003). Without DBS, the prevalence of VLa thalamic bursting has not been thoroughly explored. In MPTP-treated monkeys, bursting was observed in only about 10% of motor thalamic neurons recorded extracellularly (Guehl *et al.*, 2003). However, the great majority of these neurons exhibited rhythmic activity, which did not feature the long pauses associated with bursting but did include shorter pauses, leading to a bimodal ISI distribution; the impact of such ISIs on thalamocortical relay has not been studied. Interestingly, in these experiments, the bursting fraction did not change significantly between tremor and non-tremor periods, while rhythmic activity became more prominent with tremor. Moreover, motor thalamic oscillations predominantly occurred in the 5–7 Hz range that has been correlated with EMG activity during tremor in parkinsonian patients (Lenz *et al.*, 1988), not in the beta-band (Guehl *et al.*, 2003). In light of this result, and the recent accumulation of evidence about the prominence of enhanced oscillations in parkinsonian conditions (see above), an important direction for future investigations within this framework will be to explore the impact of oscillatory activity in GPi on thalamic activity patterns. Finally, a subsequent analysis of the same thalamic data emphasized changes in correlation structure and response specificity, rather than activity patterns, although this work excluded data from tremor episodes (Pessiglione *et al.*, 2005). It has been shown computationally that altered GPi activity patterns could impact the transfer of correlated activity from BG to thalamus across normal, parkinsonian, and DBS conditions (Reitsma *et al.*, 2011), but additional work on this topic is also needed. Clearly, a thorough investigation of bursting and oscillation properties of VLa thalamus under normal, parkinsonian, and DBS conditions, including establishing relationships between these properties, GPi activity patterns, and motor impairments, remains an important target for future work.

d. Additional computational studies

In the meantime, it is important to note that additional, purely computational studies have been performed that clarify the generality of this relay framework. These studies have explored an alternative, multi-compartmental TC cell model (Cagnan *et al.*, 2009) and a broader range of GPi burst frequencies and DBS parameters and sites (Cagnan *et al.*, 2009; Pirini *et al.*, 2009). Results obtained have been consistent with the idea that overly rhythmic inhibitory signals from GPi compromise TC relay, whereas effectively constant inhibitory signals from GPi to thalamus, which can be achieved via certain forms of BG DBS, promote effective relay.

The RT model and these subsequent studies established the theoretical importance of modifying bursting activity in the BG with DBS to achieve a more regularized input to thalamus. However, the RT model was criticized as a relatively simplified representation of the BG and, in its original formulation, it did use the controversial assumption that burst activity was generated by STN-GPe interactions. Hahn & McIntyre (Hahn & McIntyre,

2010) attempted to address these issues with the creation of a more detailed subthalamopallidal microcircuit model. Synaptic weights in the network were trained to fit *in vivo* neural firing patterns from parkinsonian monkeys, and the model system was driven by stochastically defined cortical beta rhythms. STN DBS applied to the model in the parkinsonian condition reproduced the reduction in GPi bursting found in experimental data. The Hahn and McIntyre model also predicted that regularization of GPi firing was dependent on the volume of STN tissue affected and a threshold level of burst reduction may be necessary for therapeutic effect, supporting the general hypotheses of the RT model.

6. A complementary approach: the information lesion

Around the same time that Rubin and Terman were developing their network model of DBS, McIntyre and Grill were developing models of the response of individual neurons to DBS (McIntyre *et al.*, 2004). These individual neuron models predicted that DBS generates efferent axonal activation at or near the stimulation frequency. These results led to the hypothesis that effective DBS overrides oscillatory pathological activity and replaces it with more regularized neuronal firing patterns. This concept was further expanded by Grill *et al.* (Grill *et al.*, 2004) with the introduction of the term “Informational Lesion”. Using a TC neuron model, they showed that DBS produced a frequency-dependent modulation of the variability of neuronal output, and above a critical frequency, stimulation resulted in regular output with zero variance. They then hypothesized that zero output variance is analogous to a lesion in terms of network processing of information. In other words, the logic here is that DBS replaces a pathological signal with an innocuous one; however, the question of what downstream effects were induced that made one signal problematic and the other harmless was not answered.

Excitingly, the concepts of stimulator pulse variance and the corresponding neuronal output variance were further evaluated by the Grill group with human experiments, as well as with computer models (Birdno *et al.*, 2007). In the human experiments, thalamic DBS with an average stimulus pulse rate of 130 Hz was more effective at reducing tremor when the pulses were evenly spaced than when there were large variances in the inter-pulse interval. These experiments do not reveal the mechanism underlying tremor reduction, however. In the thalamic neuron model, increasing the difference between the intra-pair and inter-pair pulse intervals rendered model neurons more likely to fire synchronous bursts, more likely to fire irregularly, and less likely to entrain to the stimulus. This observation could be consistent with an information lesion viewpoint, that the failure to entrain represents a failure to eliminate pathological “information”, or with the relay framework, that the presence of synchronous thalamic bursts compromises responses to cortical signals. Indeed, it is possible that these viewpoints are in fact the same, and that what makes signals pathological or not is determined by their impact on relay. An indication of this convergence of theories is provided by the work of Dorval *et al.* (Dorval *et al.*, 2010). These authors expanded the analysis of DBS regularity to the PD symptom of bradykinesia, showing that DBS delivered with low inter-pulse variability was more effective than irregular DBS at reducing symptoms. They then used the RT model to show that high-frequency stimulation alone is insufficient to improve relay. In summary, DBS pulses must be highly regular to be effective.

7. An alternative framework based on (de)synchronization

Various computational models relating to parkinsonian activity and/or DBS have been developed and reviewed elsewhere (Titcombe *et al.*, 2004; Modolo *et al.*, 2011). This paper does not provide a comprehensive review but instead considers a particular mechanistic theory for how parkinsonian activity could induce specific downstream effects and how

DBS could eliminate these effects. We have spelled out the assumptions underlying this theory, the consequences of these assumptions, and a set of predictions that follow. Such an elaboration of the logical structure of a theory is critical for the objective evaluation of its biological and clinical relevance. For comparison, we will now consider some of the logic underlying an alternative computational approach to parkinsonism and DBS in the extensive work of Tass and collaborators (see, e.g., Tass, 2006).

Many of the works from this group build off of the experimental observation that excessive synchronization of BG activity is a central feature of parkinsonism. The central assumption made, in light of this observation, is that the efficacy of DBS depends critically on its ability to desynchronize neurons in its target site. In other words, a key prediction on which this theory depends is that a clinical intervention that achieves desynchronization will be effective, while failure to desynchronize will correspond to persistence of parkinsonian symptoms. Note, however, that the precise meaning of these statements depends on the definition of synchrony. The models used in some works in this vein consist of phase equations. Such equations treat each neuron as an intrinsic oscillator, characterized by a time-dependent phase $\theta \in [0, 2\pi]$. Alternatively, partial or integrodifferential equations can be used to track the time evolution of the density of phases within a neuronal population treated as a continuum, or discrete equations in higher dimensions can be used to represent each neuron and a corresponding phase for each neuron can be derived, as long as each neuron exhibits regular intrinsic oscillations. Synchrony of a discrete population of phase oscillators is measured using an order parameter, $R(t)$. We note that $R(t)=0$ occurs whenever neuronal phases are equally distributed on $[0, 2\pi]$. Thus, the synchrony measure gives the same result whether neurons are fully desynchronized or they form perfectly synchronized clusters that are uniformly spaced in phase. So, activity that is still very structured can be characterized as desynchronized, and this issue must be borne in mind in considering results based on an order parameter definition of synchrony.

Starting from the assumptions that the parkinsonian BG is characterized by a stable regime of synchronized oscillations of a collection of intrinsic oscillators and that DBS works through desynchronization, Tass et al. have shown that several consequences emerge. One major consequence is that non-standard DBS paradigms may be more effective than standard high frequency DBS at achieving a non-pathological state. Indeed, Tass and collaborators have been creative in proposing a variety of DBS techniques, including two-pulse (or soft-resetting) stimulation, multisite stimulation, and delayed feedback stimulation based on LFP signals (see also, Rosenblum & Pikovsky, 2004a; Rosenblum & Pikovsky, 2004b; Tukhlina *et al.*, 2007), that work well at achieving desynchronization in their computational models. Preliminary testing in patients with some of these ideas has been promising (Tass, 2011).

Suppose, within this framework, that we make the additional assumption that there is some form of plasticity that can occur in the BG network. The parkinsonian state would have to be stable despite the presence of this plasticity. DBS, however, represents an external forcing to the system. So as long as DBS is present, the stable states of the system would likely differ from what they were without DBS. Thus, whatever quantities in the system were involved in its plasticity mechanisms could behave differently in the presence of DBS than in its absence. If DBS were subsequently removed, then the system would be in a different state than it was in before the application of DBS, such that it could possibly converge to a different state than it was in previously. This insight opens the door to the possibility that the right form of DBS, applied for a sufficient amount of time, could alter the previously parkinsonian BG in such a way that DBS would be no longer needed to avoid pathological activity.

As a specific example of this principle, Tass and collaborators consider synaptic plasticity within the BG (Tass & Majtanik, 2006; Hauptmann & Tass, 2010). Their results show that if excitatory connections are assumed to exist between pairs of neurons within the STN, and the strengths of these connections evolve via certain spike timing-dependent plasticity rules, then multisite coordinated reset stimulation (MCRS) of STN will cause these to change. Once DBS is removed, the model network is in the basin of attraction of a different stable state than it had been before DBS was applied. Thus, from its new state, the system will evolve toward a different activity regime lacking parkinsonian synchronization. Effectively, the DBS pushes the BG out of its pathological state, such that DBS is no longer needed. Alternatively, the new state that is achieved by the time that DBS is terminated may fail to be stable, but it may be sufficiently far removed from the pathological state that the return to pathology is very gradual. In this case, while DBS could not be eliminated indefinitely, its delivery could be interrupted, avoiding buildup of tissue damage, use of battery power, and induction of DBS-related side effects for some period until the pathological state is recovered to an extent that DBS is needed again.

While very appealing for its elegance and its potential to improve the how DBS is applied, this theory in its current formulation does depend critically on STDP in connections among excitatory neurons within the STN, the presence of which currently lacks experimental confirmation. It is possible that the general theory is correct but that the site of plasticity is elsewhere in BG, an idea that remains to be explored. The logic of these ideas leads to the prediction that if MCRS is applied for a period of time that effectively harnesses plasticity, then it should be possible to turn it off after this time and observe sustained elimination of symptoms. While the experimental search for the presence of long-term synaptic plasticity somewhere in the BG and for the relevance between such plasticity and the efficacy of DBS could prove arduous, the testing of this prediction about the removal of MCRS should be more immediately accessible.

10. Other effects of DBS treatment

There is a growing body of evidence suggesting that stimulation effects in the STN may not be entirely explained by effects of the stimulation on basal ganglia output. In particular, optogenetic and electrophysiologic studies in experimental animals have suggested that antidromic activation of motor cortical areas occurs and may be relevant for the clinical effects of STN DBS (Li *et al.*, 2007; Dejean *et al.*, 2009; Gradinaru *et al.*, 2009), explained by the proximity of the stimulation site in the STN to the internal capsule and the existence of the corticosubthalamic pathway. Experiments in human patients in whom cortical evoked potentials were recorded have also arrived at the conclusion that antidromic stimulation effects occur in STN DBS (Ashby *et al.*, 2001; Hanajima *et al.*, 2004; MacKinnon *et al.*, 2005; Kuriakose *et al.*, 2010; Devergnas & Wichmann, 2011). Such effects are much less likely to occur in GPi DBS, because the electrodes are positioned away from the internal capsule, and GPi does not receive direct cortical input (Devergnas & Wichmann, 2011). These antidromic effects of DBS, as well as possible downstream effects of the stimulation of fibers of passage that reach brain stem and spinal cord, have not yet been incorporated into the existing models of DBS effects, representing a significant and exciting challenge for this field. We also note that theories focusing on thalamocortical relay implicitly predict that cortical alterations will arise in parkinsonism due to compromised relay, and that STN DBS will modify these cortical effects.

11. Conclusions

We have reviewed many of the changes in activity observed in parkinsonism in animal models and human PD patients. Our review includes a discussion of the connection between

these changes and the expression of motor aspects of parkinsonism, but these relationships are currently not well understood, and much new work is needed to firmly establish the pathways through which modulations of BG activity lead to motor and other effects. A variety of computational models exist that are relevant to BG activity patterns under various conditions (e.g., tremor-band oscillations in the STN-GPe network (Terman *et al.*, 2002) and beta or other oscillations (Leblois *et al.*, 2006; Holgado *et al.*, 2010; McCarthy *et al.*, 2011), the emergence of particular clinical conditions (e.g., bradykinesia, see Cutsuridis & Perantonis, 2006; Moroney *et al.*, 2008), and the application of DBS to the parkinsonian BG (e.g., Wilson *et al.*, 2011). Some of these are reviewed elsewhere, with an emphasis on parkinsonian activity and DBS (Titcombe *et al.*, 2004; Modolo *et al.*, 2011). Rather than providing a direct review or overview of the galaxy of computational models of BG, we have provided a new perspective on the logic underlying a small number of modeling frameworks that focus on downstream effects of parkinsonian activity and possible mechanisms for the therapeutic efficacy of DBS. In particular, some of these models provide mechanistic hypotheses for how parkinsonian activity may compromise downstream thalamic function and suggest that the effectiveness of certain therapies may relate to their impact on this processing, and these ideas merit future experimental exploration. Our discussion emphasizes the key assumptions and predictions of the computational modeling approaches that we consider. A careful detailing of the logical underpinnings of computational models is crucial for their utility, since this step makes clear where experiments should be directed to attempt to falsify the hypotheses that they embody and thereby refine our understanding of the biological components that they represent.

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Abbreviations

BG	basal ganglia
CM	centromedian nucleus of the thalamus
DBS	deep brain stimulation
EMG	electromyogram
GABA	gamma-amino butyric acid
GPe	external segment of the globus pallidus
GPI	internal segment of the globus pallidus
LFP	local field potential
MCRS	multisite coordinated reset stimulation
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MSN	medium spiny neuron
PD	Parkinson's disease
PPN	pedunclopontine nucleus
RT model	Rubin/Terman model
SNc	substantia nigra, pars compacta

SNr	substantia nigra, pars reticulata
STN	subthalamic nucleus
TC	thalamocortical
VA	ventral anterior nucleus of the thalamus
VLa	anterior portion of the ventrolateral nucleus of the thalamus

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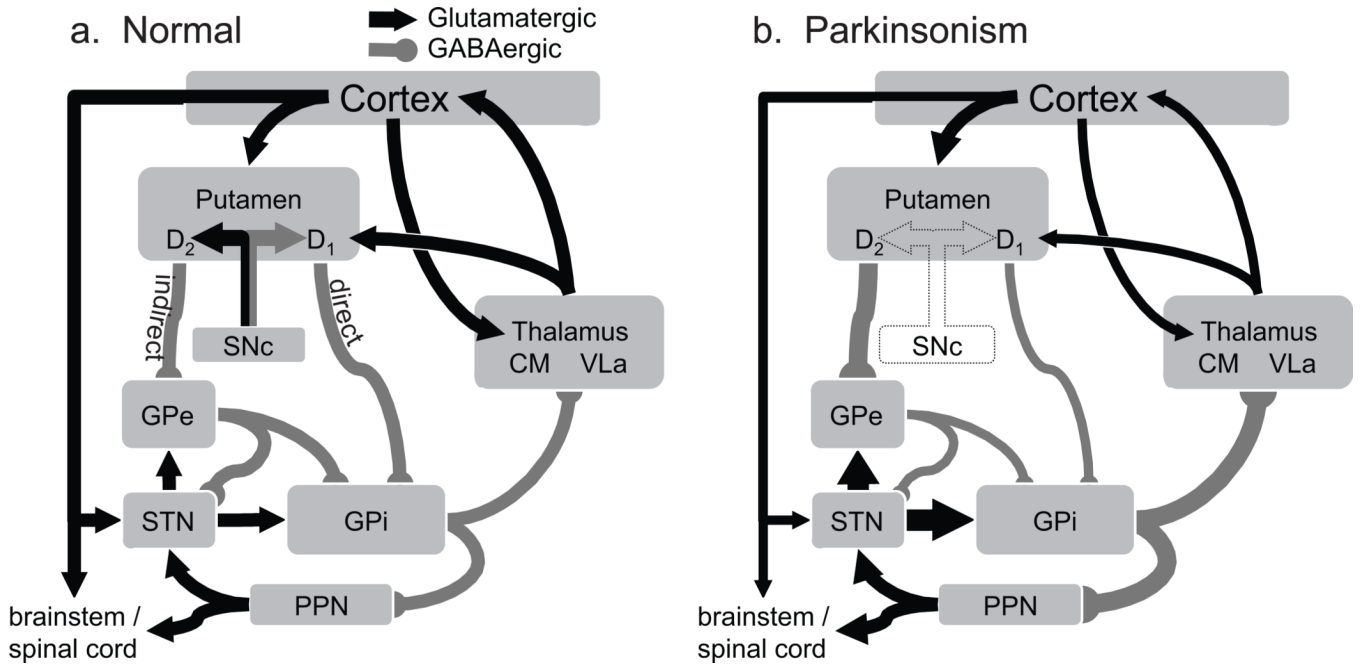


Figure 1. Circuit diagram of the BG and changes in discharge rate predicted by the standard ‘rate model’ of PD. (a) The basic loop circuit includes an excitatory glutamatergic (black arrow) projection from the neocortex to the striatum (putamen) and then inhibitory (γ -amino butyric acid-containing; *GABAergic*, gray lines) striatal projection (the ‘direct’ pathway) to the GPi. GABAergic neurons in GPi project to targets in the thalamus [VL_a and centromedian nucleus (CM), a posterior intralaminar nucleus] and the brainstem (PPN). The VL_a thalamus projects to the frontal cortex including parts of the premotor and primary motor cortex. Only principal pathways are shown for the internal connectivity of the BG. *Direct* and *indirect* pathways start in projection neurons of the putamen that express D₁- and D₂-type dopamine receptors, respectively. D₂-type neurons project to GPe. GPe projects to the STN and GPi. STN also receives monosynaptic glutamatergic input from the motor cortices and projects to GPi and GPe. Dopaminergic neurons of the SNc innervate the striatum and, less densely, the GP and STN (not shown). (b) Changes in mean discharge rate that the ‘rate model’ predicts will result from degeneration of dopamine neurons of the SNc and their terminals in the putamen. The thickness of lines indicates the predicted changes in discharge rate. The diagram does not show parkinsonism-related changes for anatomical connections that are not part of the standard rate model (e.g., corticostriatal and PPN projections). See text for abbreviations.

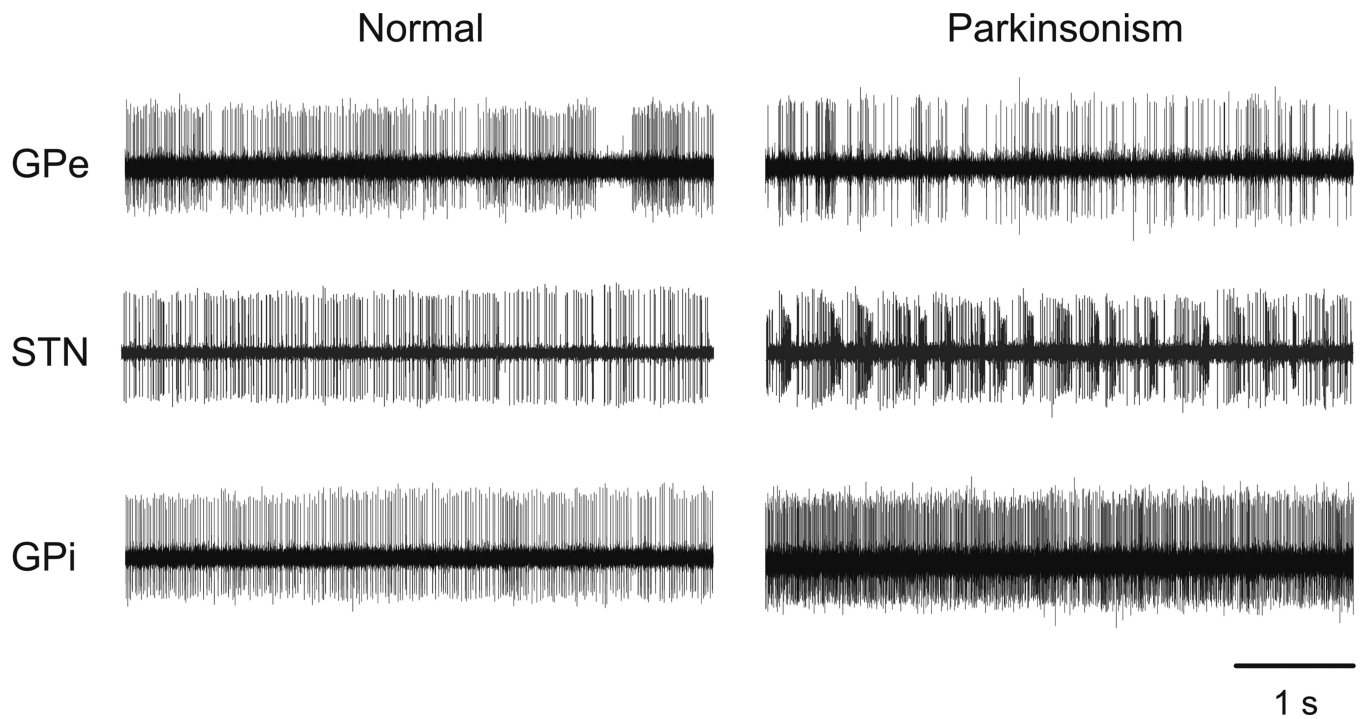
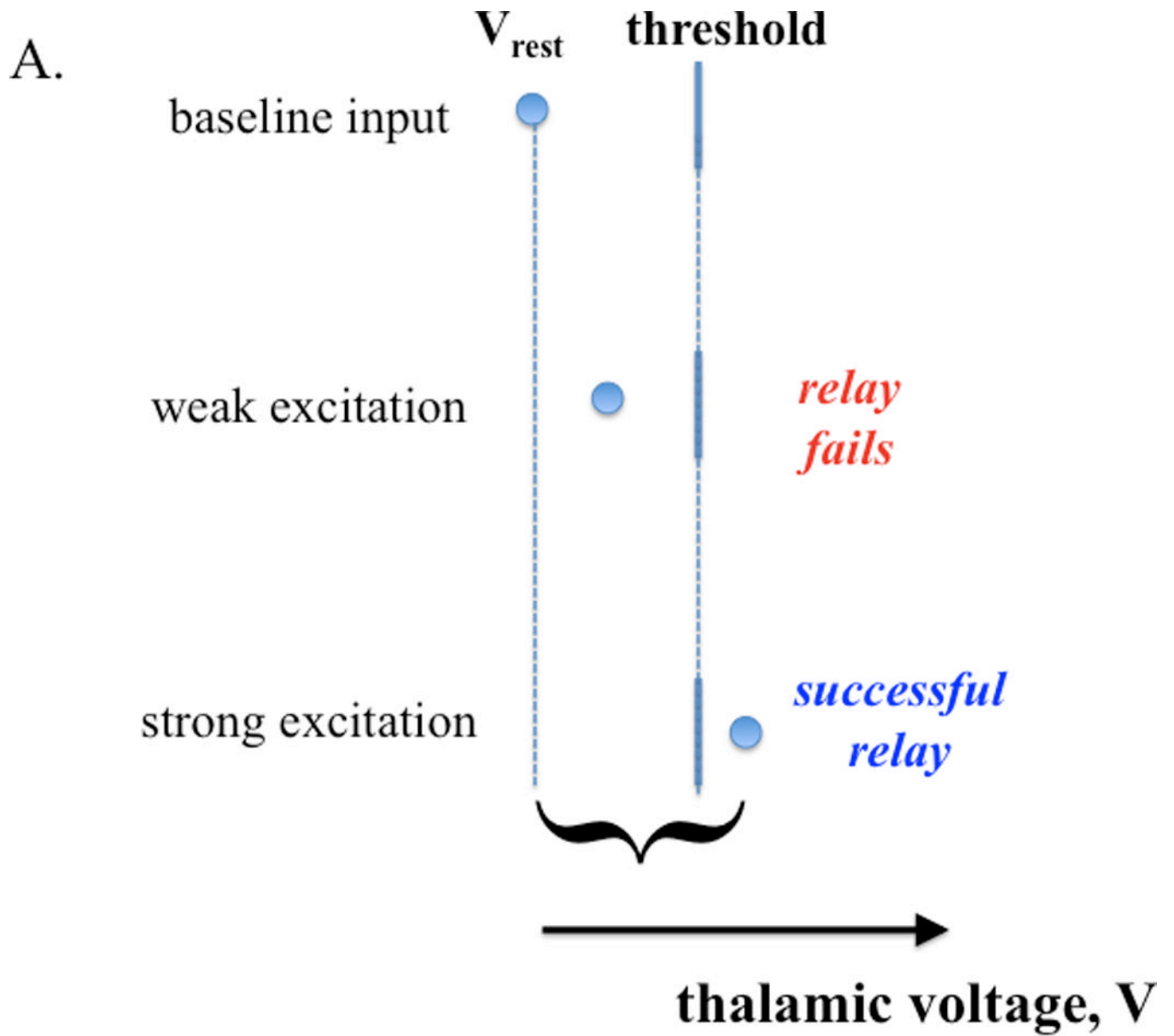


Figure 2. Changes in the activity of single cells in GPe, STN or GPi of parkinsonian monkeys. Shown are examples of separate neurons, recorded with standard extracellular electrophysiologic recording methods in normal and parkinsonian animals. Each data segment is 5 seconds in duration. Figure from Galvan and Wichmann (Galvan & Wichmann, 2008), used with permission.



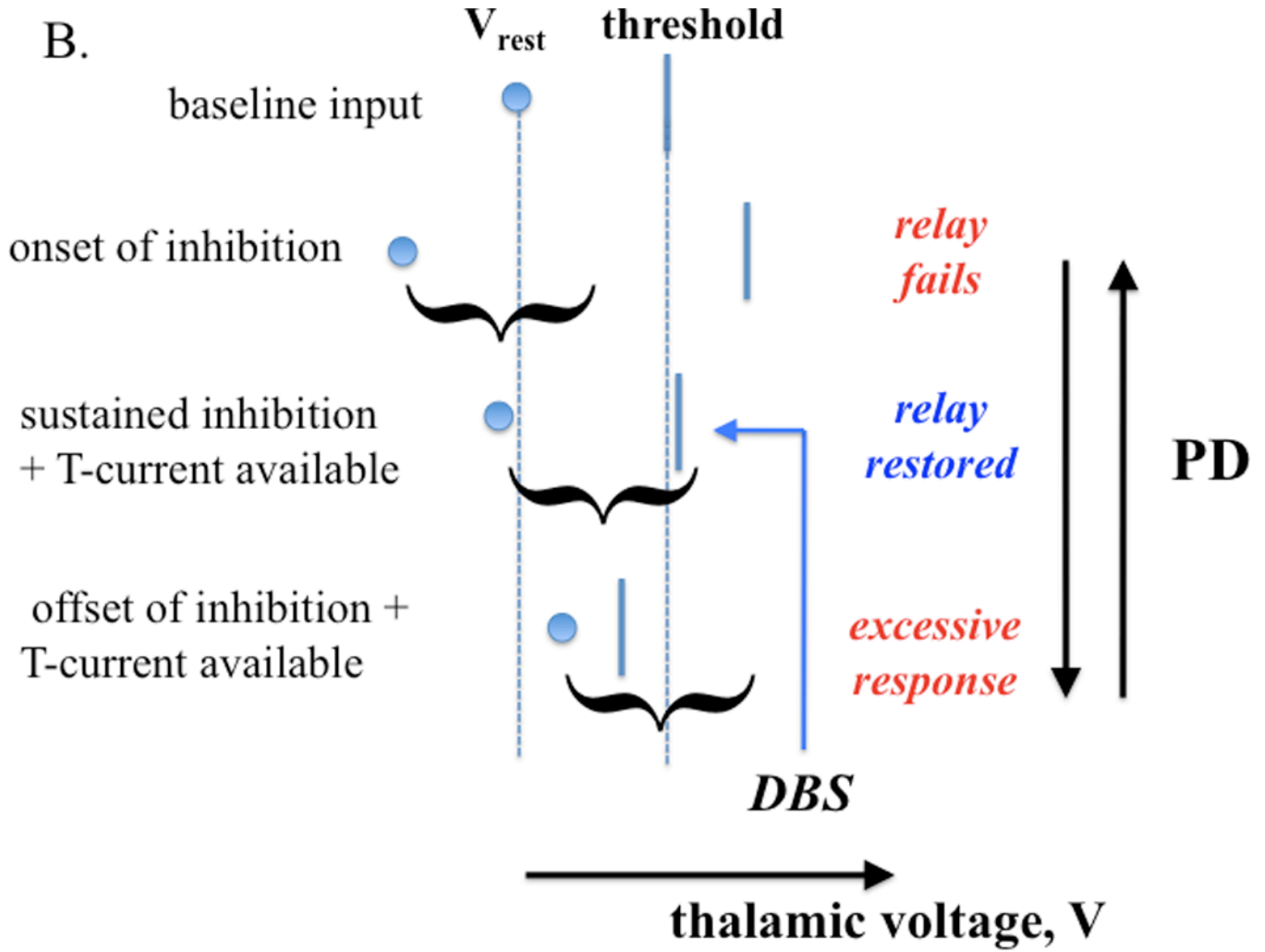


Figure 3. Inhibition influences thalamic relay capability (schematic illustration). A. Baseline input conditions establish a rest potential and a threshold for action potential generation (top). If an excitatory input arrives, a successful relay response (i.e., spike generation) is determined by the strength of that input relative to the separation between rest potential and threshold (middle, bottom); a sufficiently input strength to yield relay is represented by a curly bracket. B. Parkinsonian conditions are characterized by oscillations in the inhibitory input to thalamus (from GPi). At the onset of strong inhibition, a formerly relay-inducing excitatory input fails to yield relay (top). If inhibition is sustained, T-current deinactivation can restore relay by raising rest potential and lowering threshold (middle). Since T-current inactivation is slow, the arrival of the same input after a relatively abrupt withdrawal of inhibition can yield an excessive response (bottom). One possibility is that DBS of STN pins the inhibitory input from GPi to thalamus at a high level, where relay is restored by T-current availability.

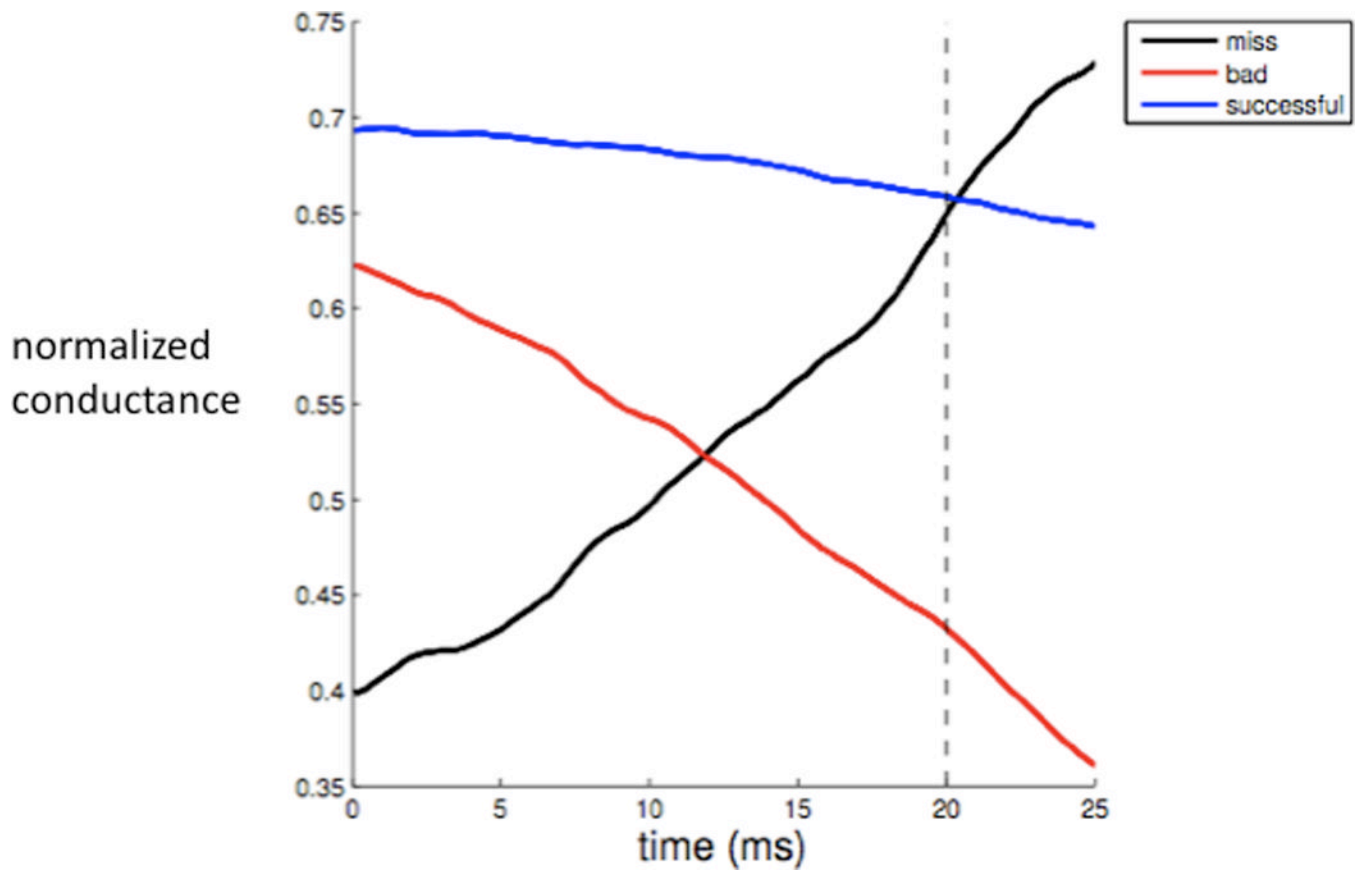


Figure 4.

Response-triggered average GPi input signals to computational model TC relay neuron. Input signal strength is measured as normalized conductance, given by synaptic conductance divided by maximal synaptic conductance. The GPi inhibitory output patterns preceding different types of TC responses to excitatory inputs are qualitatively different, consistent with the impact of relatively abrupt changes in GPi signaling on TC response capabilities (see text for details). Modified from Guo et al. (Guo *et al.*, 2008).