Common Therapeutic Mechanisms of Pallidal Deep Brain Stimulation for Hypo- and Hyperkinetic Movement Disorders.

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Abstract 230 Words

Total 10824 Words (including references)

References 183

Figures 8

Tables 0

Key words: deep brain stimulation, nonhuman primate, Parkinson’s disease, Tourette syndrome, globus pallidus

Running Title: Common therapeutic mechanisms of DBS

Acknowledgements: This research was supported by the Tourette Syndrome Association – USA, and the Korea Brain Research Institute basic research program funded by the Ministry of Science, ICT and Future Planning (No. 2231-415) to K.W.M. The monkeys used in this research were in part provided by the National BioResource Project “Japanese Monkeys” of the Ministry of Education, Culture, Sports, Science & Technology, Japan. The authors declare no conflict of interests.

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Abstract

Abnormalities in cortico-basal ganglia (CBG) networks can cause a variety of movement disorders ranging from hypokinetic disorders, such as Parkinson’s disease (PD), to hyperkinetic conditions, such as Tourette syndrome (TS). Each condition is characterized by distinct patterns of abnormal neural discharge (dysrhythmia) at both the local single-neuron level and the global network level. Despite divergent etiologies, behavioral phenotypes, and neurophysiological profiles, high-frequency deep brain stimulation (HF-DBS) in the basal ganglia has been shown to be effective for both hypo- and hyperkinetic disorders. The aim of this review is to compare and contrast the electrophysiological hallmarks of PD and TS phenotypes in nonhuman primates and discuss why the same treatment (HF-DBS targeted to the globus pallidus internus, GPi-DBS) is capable of ameliorating both symptom profiles. Recent studies have shown that therapeutic GPi-DBS entrains the spiking of neurons located in the vicinity of the stimulating electrode, resulting in strong stimulus-locked modulations in firing probability with minimal changes in the population-scale firing rate. This stimulus effect normalizes/suppresses the pathological firing patterns and dysrhythmia that underlie specific phenotypes in both the PD and TS models. We propose that the elimination of pathological states via stimulus-driven entrainment and suppression, while maintaining thalamocortical network excitability within a normal physiological range, provides a common therapeutic mechanism through which HF-DBS permits information transfer for purposive motor behavior through the CBG while ameliorating conditions with widely different symptom profiles.
**Introduction:**

High-frequency deep brain stimulation (HF-DBS) has emerged as a primary neurosurgical treatment for a number of neurological conditions refractory to drug therapy, especially for disorders arising from pathology within cortico-basal ganglia (CBG) networks. Generally, the disorders that arise from CBG abnormalities can be classified under the rubric of hypo- and hyperkinetic movement disorders. A representative example of a hypokinetic condition is Parkinson’s disease (PD), while that of a hyperkinetic condition is Tourette syndrome (TS).

Historically, the most common use of HF-DBS — a procedure in which low-impedance macroelectrodes are chronically implanted into the basal ganglia to deliver high-frequency (~150 Hz) electrical stimulation — has been for the amelioration of PD symptoms. Typically, the primary target for stimulation is the globus pallidus internus (GPi), the subthalamic nucleus (STN), or thalamus, with the STN being the most popular (Cooper et al. 1980; Benabid et al. 1987; Agid 1999; Starr et al. 1998; Rodriguez-Oroz et al. 2005; Bronstein et al. 2011; Krauss et al. 1999; Starr et al. 2004). More recently, encouraged by the success of HF-DBS in treating PD symptoms, there have been increasing attempts to apply the same procedure in basal ganglia-related hyperkinetic disorders such as TS and related tic disorders (van der Linden et al. 2002; Dehning et al. 2008; Dueck et al. 2009; Martinez-Fernandez et al. 2011; Shahed et al. 2007; Azoulay-Zyss et al. 2011; Houeto et al. 2005; Welter et al. 2010; Piedimonte et al. 2012; Martinez-Torres et al. 2009; Vandewalle et al. 1999). Studies using animal models have confirmed clinical findings that HF-DBS can ameliorate symptoms of tic disorders (Baup et al. 2008; Posch et al. 2012; McCairn et al. 2012; McCairn et al. 2013b; Angelov et al. 2014), leading to the consensus that HF-DBS can be an effective therapy for medically refractory TS.
(Schrock et al. 2015). Thus, clinical experience supports the therapeutic efficacy of HF-DBS for both hypo- and hyper-kinetic disorders. However, the question remains why the same intervention is effective against disease conditions that exhibit apparently opposing symptom profiles (i.e., hypokinetic vs. hyperkinetic) and divergent underlying pathophysiology.

To address this question, we will review the established literature for HF-DBS use in PD and parkinsonian models and compare the parallels in terms of effects and mechanisms of DBS actions with emerging data from stimulation-based therapies in TS and tic disorder models. In doing so, an emphasis will be placed on HF-DBS delivered to the globus pallidus internus (GPi), the primary output nucleus for the basal ganglia skeletomotor circuit.

Hypokinetic movement disorder pathophysiology: Parkinson’s disease.

PD is a neurodegenerative condition that is associated with the accumulation of Lewy bodies and the loss of dopaminergic neurons in the midbrain and their innervation of CBG and forebrain structures (Braak et al. 2003; Kalia and Lang 2015). There are a number of longstanding models with respect to functional changes within the CBG as a consequence of the underlying pathophysiology associated with PD, which can be extended to hyperkinetic disorders as well. Specifically, these models capture primary changes in the ‘indirect’ and ‘direct’ pathways, their effects on globus pallidus externus (GPe) and GPi, and the knock-on effects to thalamocortical networks, commonly referred to as the ‘box-and-arrow’ models (Fig. 1A) (Alexander and Crutcher 1990; Albin et al. 1989; DeLong 1990). Although several shortcomings have been pointed out as modern anatomical and physiological techniques paint a rather more complex picture, such as a disproportionate emphasis on tonic levels of activity, incapability of predicting a role of oscillatory and synchronous activity, and a focus on unidirectional information flow through the network, the theoretical framework established by those models
provides a useful starting point for discussing the latest findings related to hypo- and
hyperkinetic movement disorders and the effects of DBS.

The pallidum is a heterogeneous structure consisting of a number of different cell types
(Nambu and Llinas 1997; Mastro et al. 2014; Abdi et al. 2015; Dodson et al. 2015). The GPe acts
as a primary relay of the indirect pathway (Gerfen and Wilson 1996; Smith et al. 1998), sending
efferent projections to the STN (Francois et al. 2004; Mastro et al. 2014), the GPi (Hazrati et al.
1990; Smith et al. 1994), and to the thalamic reticular nucleus (Hazrati and Parent 1991), as well
as those back to the striatum (Beckstead 1983; Kita et al. 1999; Mastro et al. 2014). In contrast,
the GPi acts as the primary relay of the direct pathway, whose major target is the pallidal
receiving regions of the thalamus (Albin et al. 1989; Albin et al. 1995; DeLong 1990; Baron et
al. 2001; Sidibe et al. 1997; Parent and Parent 2004). Although historically the internal pathways
of the BG were conceptualized as being highly segregated, more recent studies have suggested
that such a view should be treated with caution, with collateralization of striatofugal projections
terminating in multiple targets in downstream nodes (Parent et al. 2000; Parent et al. 2001;
Levesque and Parent 2005; Cazorla et al. 2014), while functional studies suggest that co-
activation of both pathways is necessary for initiating movement (Cui et al. 2013), for review see
(Calabresi et al. 2014).

The firing properties of GP neurons, in a healthy brain, tend to show complex temporal
patterns with both segments having high population-scale mean firing rates, e.g., ~ 70 Hz in the
GPe vs. ~ 80 Hz in the GPi (DeLong 1971; DeLong 1972; Gardiner and Kitai 1992; Magill et al.
2000; Starr et al. 2005). They also tend to show a low or complete absence of any significant
low-frequency oscillatory and correlated behavior between neighboring and distant neurons in
the spectral and temporal domains (Bergman et al. 1998; Nini et al. 1995; Bar-Gad et al. 2003).
Functionally, the pallidal complex is perceived to initiate or modulate behavior by choosing one or more actions out of a multitude of actions presented to them by the cortico-striatal network (Mink 1996; Beiser and Houk 1998; Redgrave et al. 1999; Tepper et al. 2004; Isoda and Hikosaka 2007; Isoda and Hikosaka 2008). The encoding of behavioral parameters in pallidal activity is dependent on the context of the action, i.e., whether the task being performed is guided by sensory cues, memory, or involves specific goal directed and spatial/object characteristics (Turner and Anderson 2005; Arimura et al. 2013; Hoshi 2013; Jin et al. 2014). It should be noted that pallidal processing is also modulated by inputs from the ‘hyperdirect’ pathway which originates in the cortex and directly synapses within the STN (Nambu et al. 2000; Nambu et al. 2002; Chu et al. 2015; Mastro and Gittis 2015).

A long-held view on the pathophysiology of hypokinetic conditions in PD (e.g., akinesia) is that tonic firing rate changes occur at critical nodes in CBG network (Albin et al. 1989; DeLong 1990). Specifically, the box-and-arrow model predicts that the absence of dopamine tips the balance between the two intrinsic pathways so that indirect pathway MSNs and direct pathway MSNs, respectively, increase and decrease their influence on the output nuclei of the basal ganglia. This imbalance leads to increased tonic inhibitory outflow from the GPi to the thalamus, which in turn reduces thalamocortical excitability (Fig. 1A). There is indeed experimental evidence that supports this prediction (Starr et al. 2005; Pasquereau and Turner 2011), while manipulation of the two pathways through optogenetic stimulation can induce or relieve parkinsonian symptoms (Kravitz et al. 2010).

The conceptual idea that changes in tonic firing rate can account for the symptoms associated with PD is attractive due to its simplicity – excessive inhibitory BG output leads to decreased cortical activity and thus decreased motor output. However, there are a number of
other hypotheses as to why PD symptoms might develop. These emphasize spatiotemporal
dynamics of cellular firing, including excessive oscillatory and synchronous activity in the alpha
(7 – 12 Hz) and beta (13 – 30 Hz) frequency range commonly referred to as low-frequency
oscillations (LFO), burst firing, and a breakdown of functional segregation in the CBG network
(Filion and Tremblay 1991; Raz et al. 2000; Goldberg et al. 2002; Goldberg et al. 2004;
Hutchison et al. 1994; Hutchison et al. 2004; Wichmann et al. 1999; Soares et al. 2004; McCairn
and Turner 2009; Pasquereau and Turner 2011; McCairn and Turner 2015; Stein and Bar-Gad
2013) (Fig. 1B). Among the potential neuronal abnormalities, it is perhaps excessive LFO and
synchronous activity in the temporal and spectral domain that has received most attention in
recent years as the primary causal factor in the emergence of the anti-kinetic state in PD (Fig.
2A). Thus, excessive synchrony and pathological LFO in the output nuclei of the basal ganglia is
hypothesized to inhibit voluntary initiation of movement by exerting an impact on basal ganglia-
recipient motor centers, such as cortical motor areas (Marsden et al. 2001b; Brown et al. 2004b).

Hyperkinetic movement disorder pathophysiology: Tourette syndrome.

TS has been recognized as a discrete clinical condition for over a century (Gilles de la
tourette 1885). There are a number of key neurotransmitters that are hypothesized to play a role
in the condition, including excess dopamine and decreased GABA (McCairn and Isoda 2013). It
is generally thought that TS involves focal abnormalities within the basal ganglia, particularly
the striatum, which directly affect the indirect and direct pathways (Peterson 2001; Mink 2001;
Albin and Mink 2006; Mink 2003; McCairn et al. 2013a; Israelashvili et al. 2015) . Presumably,
such abnormalities of the striatum arise as a consequence of dysfunctional GABAergic and
cholinergic networks (Kalanithi et al. 2005; Kataoka et al. 2010; Lerner et al. 2012; Draper et al.
2014; Xu et al. 2015) due to a combination of complex genetic factors (Grados and Mathews
The spectrum of TS symptoms is wide-ranging; it includes motor, cognitive, and emotional abnormalities, suggesting that TS-related abnormalities affect all the functional territories (i.e., motor, associative and limbic) of the CBG networks. Expressed behaviors range from simple motor tics and complex motor behaviors such as abnormal vocalization, to neuropsychiatric abnormalities generally manifesting as obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) (The Tourette Syndrome Classification Study Group 1993).

In TS, the box-and-arrow model predicts that there should be a decrease in GPi output and excessive excitability in thalamocortical circuits for the expression of tics (Fig. 1). Direct recording from GPi neurons in human TS patients shows some evidence for decreased pallidal outflow (Zhuang et al. 2009; Alam et al. 2014) and excess LFO (Marceglia et al. 2010; Zauber et al. 2014), indicating that both rate firing, as predicted by box-and-arrow-models, and synchronous oscillatory activity contribute to the condition. Other studies using a nonhuman primate model of TS demonstrate persistent, periodic changes in activity within CBG networks (McCairn et al. 2009; Worbe et al. 2009; Bronfeld et al. 2011; McCairn et al. 2013b; McCairn et al. 2012) and cerebellar networks (McCairn et al. 2013c) that phasically match predictions from classical box-and-arrow models. In these animal studies, the GABA antagonist bicuculline is microinjected into the motor territory of the putamen in order to induce periodic muscular contractions, recapitulating one of the primary symptoms of TS – simple myoclonic tics. Associated with these behaviors, periodic activations in EMG activity emerge that are driven by abnormal spiking activity in the striatum, pallidum and related CBG structures (Fig. 2B).

To summarize, although both PD and TS are complex neurological conditions, the emergence of differing symptom profiles can be envisaged to arise from abnormalities in BG...
processing. Specifically, within the striatum PD is thought to arise through a loss of DA innervation, while in TS excess influence from dopamine coupled with abnormalities in GABAergic transmission leads to uncontrolled movements and behaviors. These unwanted behaviors are primarily a result of imbalance between the indirect and direct pathways that originate from within the striatum, and points to critical role for the output nuclei of the BG and their effect on downstream networks.

Globus pallidus internus deep brain stimulation.

The premise for using stimulation-based therapies targeting the GPi stems from surprising observations that lesions intentionally made in the GPi, a neurosurgical procedure called pallidotomy, could ameliorate many of the symptoms associated with PD (MEYERS 1951). Although pallidotomy as a treatment option has fallen in and out of favor several times, for review see (Guridi and Lozano 1997), it remains a practiced neurosurgical technique for the treatment of drug-refractory PD (Laitinen et al. 1992; Lozano et al. 1995; Baron et al. 1996). However, due to its irreversibility, pallidotomy has been gradually superseded by stimulation-based therapies that target the same region.

Due to the similarity of the therapeutic response between GPi-DBS and pallidotomy for PD-like movement disorders, early theories about the mechanism of action proposed that GPi-DBS works by inhibiting neuronal activity in the vicinity of the stimulating electrode, leading to the prevailing view that GPi-DBS is essentially a reversible, functional pallidotomy. This stimulation-induced inhibition of the Gpi would reverse the pathological output from the basal ganglia, thereby normalizing activity in thalamocortical networks. There have been numerous clinical reports on the effectiveness of HF-DBS targeting the Gpi for both PD (Rodriguez-Oroz et al. 2005; Bronstein et al. 2011) and TS (Ackermans et al. 2012; Schrock et al. 2015). The
efficacy of DBS has been shown to be dependent on a number of critical stimulation related
variables, including frequency, amplitude, polarity, pulse width, and pattern of stimulation
(Rizzone et al. 2001; Kuncel et al. 2006; Birdno and Grill 2008; Birdno et al. 2012; Dorval et al.
2010).

Critically, Gpi-DBS has been shown to be effective for nonhuman primate models of PD
(Fig. 3A) (Boraud et al. 1996; McCairn and Turner 2009; Johnson et al. 2012) and TS (Fig. 3B)
(McCairn et al. 2013b; McCairn et al. 2012). Therefore, it is possible to assess therapeutic
correlates of pallidal single-unit responses during targeted stimulation in well controlled animal
test platforms. Direct measurement of the impact of Gpi-DBS on firing rate changes shows that
stimulation induces a number of response patterns in both PD and TS models (Fig. 4A). In
support of the general inhibition hypothesis, a subset of neurons respond with reductions in firing
rates (Fig. 4B), while others can show near complete inhibition (Fig. 4C) (Benazzouz et al. 1995;
Boraud et al. 1996; Dostrovsky et al. 2000; Wu et al. 2001; McCairn and Turner 2009; Bar-Gad
et al. 2004; Erez et al. 2009; Liu et al. 2012; Chiken and Nambu 2013). These rate changes are
probably not a product of depolarization-block or voltage-gated current inactivation (Beurrier et
al. 2001), because it is possible to detect action potentials with no amplitude attenuation during a
period of sustained reductions (McCairn and Turner 2009). The observed inhibition is most
likely due to stimulation-evoked GABA release (Chiken and Nambu 2013), as GABAergic
afferents collateralize so extensively in both pallidal segments (Parent et al. 1995; Nambu et al.
1997; Sato et al. 2000a).

However, in contrast to the prediction made by the inactivation hypothesis, it is
commonly observed in monkeys that during Gpi-DBS, individual neurons in both segments of
the pallidum show large and persistent increases in firing rate in PD (McCairn and Turner 2009;
Bar-Gad et al. 2004; Erez et al. 2009; Agnesi et al. 2013) and TS models (Fig. 4C and 4D) (McCairn et al. 2013b; McCairn et al. 2012). An interesting observation during delivery of GPi-DBS is that stimulus-driven cells can often show a decrementing waveform profile as stimulation progresses, as seen in the example from the TS model GPe waveform trace (Fig. 4A). This effect is also reported in another study (Hashimoto et al. 2003; McCairn et al. 2012). The mechanism for this amplitude reduction might be a form of partial depolarization blockade (Hollerman et al. 1992), indicating that prolonged stimulation might drive neuron to a point where the membrane properties can no longer respond to delivered pulses or synaptic input. The key point is that in both PD and TS models, it is possible to find a mix of effects that include inhibition and excitation in both segments of the GP in response to GPi-DBS.

The observation of increased firing rates is consistent with the finding that neurons in the downstream efferent-recipient nuclei of the thalamus exhibit reduced firing rate (Anderson et al. 2003; Montgomery 2006). In addition to direct electrophysiological evidence of HF-DBS driving individual pallidal neurons, experimental reports of changes in neurotransmitter concentrations (Windels et al. 2000; Stefani et al. 2005) as well as neuroimaging findings (Jech et al. 2001; Hershey et al. 2003; Boertien et al. 2011) support the premise that HF-DBS actively drives neurons and axons (Johnson and McIntyre 2008; McIntyre et al. 2004a; Miocinovic et al. 2006). Therefore, inhibition is only a subcomponent of any therapeutic mechanism. It is also important to note that although GPi-DBS induces several distinct types of response at the level of individual pallidal neurons (Fig. 4), the population-scale firing rate is virtually unchanged or only modestly affected during stimulation (Bar-Gad et al. 2004; McCairn and Turner 2009; Erez et al. 2009; McCairn et al. 2013b; Agnesi et al. 2013). This result is also replicated in PD patients receiving therapeutic levels of GPi-DBS (Cleary et al. 2013). We posit that this maintenance of
population-scale firing rates, at the output of the node of the BG, is a critical component of any therapeutic response. Maintenance of downstream network activity within a physiologically normal range preserves the ability of the network to continue to encode behaviorally relevant activity, a phenomenon that has recently been demonstrated in monkeys (Agnesi et al. 2013; Zimnik et al. 2015).

A consistent feature of GPi-DBS is the induction of fast multiphasic changes in firing rate during interpulse intervals in both segments of the pallidum. The multiphasic responses can be broken down into discrete events: short-latency (< 2 ms) phasic excitation in a manner consistent with antidromic driving, later-latency (3-5 ms) phasic excitation, and intervening periods of inhibition. These polyphasic responses are present in both PD (Fig. 5A) and TS (Fig. 5B) patients and models (Bar-Gad et al. 2004; McCairn and Turner 2009; Erez et al. 2009; McCairn et al. 2013b; Agnesi et al. 2013; Cleary et al. 2013), and are predicted from modeling studies of pallidal membrane ion channel properties and kinetics (Johnson and McIntyre 2008).

The early-onset antidromic effects are clear in both disease conditions (McCairn and Turner 2009; McCairn et al. 2013b) and have been predicted by studies investigating the direct effects of electrical fields on neural tissue (Ranck, Jr. 1975) as well as by modeling studies (McIntyre et al. 2004a; McIntyre et al. 2004b). It has been demonstrated that direct activation of Na\(^+\) channels is the key ion-channel mechanism for this fast-latency response (Johnson and McIntyre 2008). The reduction of firing rate that immediately follows the first and second phase of excitation is most likely ascribed to the refractory period of the activated neurons. Other contributing factors to the intervening inhibition can include the activation of GABAergic afferents from the striatum (Hedreen and DeLong 1991; Parent and Hazrati 1995; Parent et al.
2000; Parent et al. 1995), those from the other pallidal segment (Parent et al. 1995; Nambu et al. 1997; Sato et al. 2000a; Chiken and Nambu 2013), and local axon collaterals.

The later excitatory component of the multiphasic responses may be mediated by a variety of mechanisms and pathways. It could be a consequence of driving collateralized glutamatergic afferents from the STN (Sato et al. 2000b; Moran et al. 2011), while post-inhibition rebound may also be a contributing factor (Nambu and Llinas 1994). In addition to these intrinsic basal ganglia pathways, extrinsic networks, such as corticostriatal, corticosubthalamic, thalamostriatal (DeLong and Wichmann 2007), and pontinepallidal (Gonya-Magee and Anderson 1983; Scarnati et al. 1988) pathways can also play a part. A modelling study of ion-channel kinetics also suggests that an interplay between Na\(^+\) and K\(^+\) channels mediates much of the second excitatory phase within the interpulse period: that is, altering Na\(^+\) or K\(^+\) can lead to a tuning effect on the temporal dynamics of the later excitatory response (Johnson and McIntyre 2008).

If entrainment constitutes a component of the therapeutic mechanism, is it possible to claim that even low-frequency stimulation could provide some beneficial clinical effects? Several studies have demonstrated that low-frequency stimulation at therapeutic amplitudes, or high-frequency stimulation at sub-therapeutic amplitudes, can induce entrainment either locally or downstream from the stimulated nucleus, however, the entrainment tends not to be as pronounced as with therapeutic levels (Hashimoto et al. 2003; Johnson et al. 2009; Agnesi et al. 2013). Also stimulation at lower frequencies, especially in the range of the oscillations associated with the disorder, can induce a worsening of clinical symptoms (Timmermann et al. 2004; Chen et al. 2007; Eusebio et al. 2008). Low-frequency stimulation also induces parkinsonian-like blink abnormalities in intact animals (Kaminer et al. 2014). Presumably,
driving CBG networks that already overexpress oscillations in the pathological range merely exacerbates any impact these abnormal oscillations have on an already impaired system. Likewise, sub-therapeutic amplitude stimulation seems unlikely to affect individual neural elements enough to prevent propagation of abnormal signals through the network.

**GPi-DBS mediated suppression of pathological dysrhythmia**

It is noteworthy that GPi-DBS induces similar single-unit responses in both PD and TS models despite their apparent differences in disease phenotype. Specifically, once stimulation is activated, a wave of neural excitation and inhibition occurs in rapid succession in both segments of the pallidum. This multiphasic response emerges in parallel with the cessation of the pathological activity characterizing each modeled disorder and the alleviation of behavioral symptoms. With respect to the PD model, GPi-DBS significantly suppresses excess LFO in both the GPe and GPi, while inducing clinically measurable reductions in muscular rigidity (Fig. 6A). This effect occurs along with the emergence of a high-frequency component in affected spike trains (Fig. 6B) and the elimination of LFO synchrony (Fig. 6C) (McCairn and Turner 2009). Similar effects have been observed with STN-DBS in parkinsonian monkeys (Meissner et al. 2005; Moran et al. 2012) and in dystonic hamsters (Leblois et al. 2010). The suppression of oscillatory and synchronous activity is also observed in the primary motor cortex of monkeys (McCairn and Turner 2015) and rodents (Li et al. 2012), and has been inferred from studies in PD patients (Marsden et al. 2001a; Brown et al. 2004a; Hammond et al. 2007; Eusebio et al. 2011). With respect to the TS model, GPi-DBS is capable of suppressing the periodic, phasic activations in the GPe (Fig. 7A) and phasic inhibitions in the GPi that drive tics (Fig. 7B) (McCairn et al. 2013b; McCairn et al. 2012). Therefore, the reduction/modulation of aberrant neural discharge occurs in both segments of the GP in both disease conditions. These findings
suggest that GPi-DBS has a versatile mechanism for the elimination of abnormal network activity responsible for basal ganglia-mediated movement disorders, be their phenotype hypokinetic or hyperkinetic.

An emerging consensus that takes into account the multitude of single-unit effects in models and patients posits that HF-DBS induces an “informational lesion” in CBG circuits. The premise behind this theory is that activity, both normal and pathological, is prevented from transmitting through BG output nodes due to the induction of regularized and suppressed firing patterns in stimulation effected neurons, leading to reduced information-carrying capacity of spontaneous neuronal activity (Grill et al. 2004; Garcia et al. 2005; Dorval et al. 2008; Dorval et al. 2010; McIntyre and Hahn 2010; Rubin et al. 2012; Chiken and Nambu 2013). As a robust model of the network effects of HF-DBS, the “information lesion” hypothesis is dependent on observations of stimulation entrained neuronal activity, especially in the output nuclei of the BG, being entirely composed of stimulation-mediated responses, be it either entrainment or suppression. Recent studies have demonstrated, however, that during HF-DBS (targeting either GPi or STN) the GPi is still capable of encoding limb-associated movement kinematics (Agnesi et al. 2013; Zimnik et al. 2015), albeit to a lesser extent, indicating that any information lesion, should it exist, is only partial or at least highly selective.

In light of the preservation of behaviorally relevant information while suppressing unwanted pathological dysrhythmia, it would appear that HF-DBS can be thought of more as an “information filter”, as has been posited very recently (Rosenbaum et al. 2014; Zimnik et al. 2015), which disrupts abnormal information flow (Chiken and Nambu 2015; Israelashvili et al. 2015). This filtering/disrupting property operates through multiple mechanisms; however, we propose that these mechanisms, i.e., entrainment and suppression, are dependent on the
maintenance of thalamo-cortical activity within a normal physiological range, as indicated by minimal changes in population-scale firing rates in BG output nuclei and downstream recipient regions. One can consider in the case of suppression/inhibition, that if GPi neurons are tonically suppressed, they would be no longer capable of relaying pathological discharge originating from the striatum to their efferent targets. However, such a continuous suppression of GPi neurons would then release, via disinhibition, miscellaneous cortically-issued motor programs that may interfere with ongoing purposive motor behavior. One can also consider that if GPi neurons are forcibly excited at the unusually high firing rate via entrainment with DBS pulses, they are again incapable of transmitting aberrant incoming signals to their efferent targets. However, such a continuous excitation of GPi neurons would then non-selectively inhibit cortically-driven motor programs that are necessary to control purposive motor behavior. We conjecture that stimulation frequency-dependent entrainment and suppression, in parallel with a negligible impact on the population-scale firing rate, while maintaining the ability to continuously encode normal behavior in the context of relatively normal thalamocortical excitability, is an ideal condition to both achieve therapeutic effects and minimize adverse effects (Fig. 8). That is, the conduction of low-frequency pathological signals would be blocked in the pallidum by the high-frequency, periodic alternation of excitation and inhibition, thereby successfully eliminating aberrant discharge in basal ganglia-recipient networks. The minimal effect on the population-averaged firing rate would allow for the maintenance of the basal ganglia output tone within the physiological range, whereby cortical motor areas can properly issue necessary motor programs to subcortical structures such as the brainstem and spinal cord.
Conclusion

In summary, the effects of GPi-DBS on pallidal single-neuron activity are surprisingly similar between hypokinetic and hyperkinetic movement disorders. HF-DBS induces complex patterns of excitation and inhibition, and this multiphasic response is capable of suppressing abnormal dysrhythmia and synchrony in PD models, while the same effect normalizes the pathological phasic discharge that drives motor tics and, presumably, excess LFO as well in TS models. Importantly, such multiphasic responses have minimal effects on the population-scale mean firing rate of pallidal neurons. We propose that GPi-DBS-mediated activity in BG output instantiates a high-pass/low-cut filter with respect to ongoing pathological activity. Thus, GPi-DBS can minimize deleterious low-frequency reverberations in downstream networks, while artificially inducing a ‘least pathological encoding’ that permits task-related information flow through the maintenance of thalamocortical excitability. GPi-DBS has been proven to be effective in both PD and TS. With the continuing use of basic research in model systems, we hope that future research will continue to refine and improve the clinical effectiveness of this vital surgical treatment.
Figure 1: **Representation of the intrinsic pathways of the basal ganglia.** The schematic shows the ‘indirect’ and ‘direct’ pathways in the normal condition (black), and compares the relative strength (line thickness) and sign (inhibitory vs. excitatory) of the information flow as predicted by ‘box-and-arrow’ models for hypokinetic/parkinsonism (red) and hyperkinetic/tourettism (green). Note the relative changes coming from the output nucleus of the BG (GPi) and the effects on motor cortical excitability. (B) Schematic illustrating how firing patterns, e.g., synchrony and oscillatory changes, are proposed to contribute to pathological behavior in hypo- and hyperkinetic disorders. In the normal GPi (top), neurons encoding physiological movement (non-filled) transiently decrease activity, while surrounding neurons maintain asynchronous firing patterns and normal levels of burstiness. In the parkinsonian condition (middle) there is an increase in low-frequency oscillatory activity (indicated by sinusoids), synchronous spike-to-spike firing, and burstiness, with a reduction in neurons encoding for normal movement. With tourettism (bottom) there is a large increase in the number of neurons simultaneously encoding an extended action-release signal.

Figure 2: **Examples of pathological activity in the pallidum for hypo- and hyperkinetic disorders.** (A) Raw neuronal traces from the GPe and GPi taken from a parkinsonian nonhuman primate. Note the increased power in the alpha (7-12 Hz) and beta (12-30 Hz) frequency bands (red shading). These spike trains often show pronounced crosscorrelated activity in the temporal (bottom left) and spectral (bottom right) domains. The figure is adapted from (McCairn et al. 2011); all experimental procedures were completed with IACUC approval. (B) Example of myoclonic tic activity in the arm of a nonhuman primate, with associated EMG traces and raw
neuronal recording of pallidal activity. Note the propensity for increases in the GPe (raster bottom left) and decreases in GPi (raster bottom right) (adapted from (McCairn et al. 2013c)).

Figure 3: Therapeutic effects in nonhuman primates of pallidal deep brain stimulation. (A) An example of a measure of muscular rigidity (upper trace) acquired through a reactive torque motor on and off GPi-DBS. The trace shows the angular displacement of a manipulandum which moves the arm $\pm 20^\circ$, plus a measure of instantaneous torque required to move the arm through the angular displacement. During GPi-DBS there is a significant decrease in the 'work' required by the torque motor to move the arm through the angular displacement (lower panel). This reduction in torque is an indirect measure of muscular rigidity (adapted from (McCairn and Turner 2009). (B) GPi-DBS induced reduction in the amplitude of myoclonic tics induced by bicuculline injection to the sensorimotor putamen. The top panel shows a raw rectified EMG trace during 8 episodes of 30 seconds of stimulation (solid grey bars) from one monkey. The lower trace shows the mean amplitude of the tic associated EMG off (black trace) vs. on (grey trace) stimulation. Note the large reduction in tic amplitude during the on-stimulation condition (adapted from (McCairn et al. 2012)).

Figure 4: Effects on pallidal neuronal activity following GPi-DBS. (A) Raw neuronal traces acquired from the pallidum in monkey models of parkinsonism and tourettism. The traces illustrate the different types of response that can be observed in response to GPi-DBS. Perievent histograms aligned to the onset of GPi-DBS for each of the examples shown in A are presented below. (B) PD-GPe unit shown in A which shows a partial reduction in firing rate activity. (C) An example of almost complete cessation of firing activity observed in the PD-GPi. (D) Example
of TS-GPe which shows an initial increase in activity that subsides while stimulation is active.

(E) A TS-GPi neuron which shows an initial inhibition and then increased firing rate which persists beyond the cessation of GPi-DBS. Note that each of the different firing pattern responses to GPi-DBS can be found in each segment of the pallidum in both disease models (adapted from (McCairn and Turner 2009; McCairn et al. 2012)).

Figure 5: Short-latency entrainment of the pallidum following GPi-DBS. (A) Examples of interpulse changes in firing rate for individual neurons (color matrix) and population scale changes in firing rate for each segment of the pallidum in a parkinsonian model. Note the prominent peaks and troughs in the mean averages which indicate stimulus driven excitation and inhibition. (B) Multiphasic entrainment of pallidal neurons in a model of tourettism (same format as A); note the distinct peaks and troughs in both GPe and GPi, similar to parkinsonian models, which indicates stimulation driven modulation of firing activity (adapted from (McCairn and Turner 2009; McCairn et al. 2012)).

Figure 6: GPi-DBS mediated suppression of low-frequency oscillations in a parkinsonian model. (A) Perievent (DBSon) measure of torque (upper panel) aligned to perievent spectrograms of GPe (middle panel) and GPi (lower panel) firing activity. Note the suppression of oscillatory (∼10 Hz) activity in both pallidal segment as GPi-DBS starts and the subsequent reduction in torque required to move the arm (reduced yellow and green intensity) in the torque trace (adapted from (McCairn and Turner 2009; McCairn et al. 2011)). (B) Power spectral density plot showing the induction of high-frequency resonance induced by short term entrainment with the stimulation pulse, and a subsequent reduction of low frequency oscillations.
(C) GPi-DBS suppresses low-frequency coherence, a key marker of synchrony, between pairs of simultaneously recorded neurons (adapted from (McCairn and Turner 2009; McCairn et al. 2011)).

Figure 7: **GPi-DBS mediated suppression of tic related phasic changes in the pallidum.** Plots showing the response of each tic-responsive cell in the GPe (A) and GPi (B) in the off-stimulation (upper matrix) and on-stimulation (lower matrix) condition. Note the prevalence of excitatory (GPe) and inhibitory (GPi) responses in the off-stimulation condition, and their reduction during GPi-DBS. The mean activity changes for the population of GPe and GPi neurons during off-stimulation (black trace) and on-stimulation (red trace) are shown below. P values are shown below to indicate significant differences between the two stimulation conditions (adapted from (adapted from (McCairn and Turner 2009; McCairn et al. 2011)).

Figure 8: **GPi-DBS mechanism of action.** Schematic illustration of a proposed mechanism of action for GPi-DBS. The top panel illustrates how pallidal outflow, when corrupted by synchronous, low-frequency pathological dysrhythmia, leads to hypo or hyperkinetic condition that is underlined by abnormal thalamocortical excitability. Line thickness represents the relative weight of inhibitory/excitatory output from each node. The lower panel illustrates how GPi-DBS, through stimulation driven entrainment, induces a high-pass, low-cut filter in basal ganglia output (GPi), followed by an induction of least pathological encoding in GPi-thalamic pathways, leading to a
normalization of thalamocortical excitability and a maintenance of functional kinematic encoding for normal behavior.


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**A**

Rate firing model

- **Striatum**
  - GABA (Inhibitory)
  - Indirect
  - Direct

- **GPe**
  - GABA (Inhibit)
  - -ve sp/s

- **GPi**
  - GABA (Inhibit)
  - +ve sp/s

- **STN**
  - Glutamate (Excite)
  - -ve sp/s

- **Thalamus**
  - Glutamate (Excite)
  - +ve sp/s

- **Motor Cortex**
  - Glutamate (Excite)
  - -ve sp/s

**B**

Dysrhythmia/synchrony model

- **GPi**
  - Normal
  - +ve sp/s
  - Kinematic Encoding
  - Spikes
  - Bursts

- **GPi**
  - Parkinsonian

- **GPi**
  - Tourettism

**Normal Behavior**

- Tourettism
- Parkinsonism
GPi Abnormal

Thalamus Abnormal

MCx Abnormal

GPi Stimulated

Thalamus Stimulated

MCx Stimulated

~150 Hz

Low-frequency Pathological Encoding

Dysrhythmic Thalamocortical Excitability

Decreased inhibitory tone

Increased excitatory tone

Decreased excitatory tone

Increased inhibitory tone

Distrupted Kinematic Encoding

Functionally Restored Kinematic Encoding

Tourettism

Parkinsonism

DBSoff

DBSon

High-pass filter induction

Novel Minimally Pathological Encoding

Normalized Thalamocortical Excitability

Decreased inhibitory tone

Increased excitatory tone

Decreased excitatory tone

Increased inhibitory tone