# Disrupting neuronal transmission: mechanism of DBS?

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Applying high-frequency stimulation (HFS) to deep brain structure, known as deep brain stimulation (DBS), has now been recognized an effective therapeutic option for a wide range of neurological and psychiatric disorders. DBS targeting the basal ganglia thalamo-cortical loop, especially the internal segment of the globus pallidus (GPi), subthalamic nucleus (STN) and thalamus, has been widely employed as a successful surgical therapy for movement disorders, such as Parkinson's disease, dystonia and tremor. However, the neurophysiological mechanism underling the action of DBS remains unclear and is still under debate: does DBS inhibit or excite local neuronal elements? In this review, we will examine this question and propose the alternative interpretation: DBS dissociates inputs and outputs, resulting in disruption of abnormal signal transmission.

**Keywords: deep brain stimulation, basal ganglia, subthalamic nucleus, globus pallidus, cortico-basal ganglia loop, electrophysiology**

## INTRODUCTION

Applying high-frequency electrical stimulation (HFS) to a specific target in subcortical structures, known as deep brain stimulation (DBS), was introduced as a surgical treatment for movement disorders in early 1990s (Benabid et al., 1991, 1994; Siegfried and Lippitz, 1994a,b; Limousin et al., 1995). Since then, DBS has been widely accepted as an effective therapeutic option. DBS targeting the ventral thalamus dramatically alleviates essential and resting tremor (Benabid et al., 1991, 1996; Siegfried and Lippitz, 1994b; Koller et al., 1997; Rehncrona et al., 2003). DBS targeting the subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi) has been largely used for treatment of Parkinson's disease, and GPi-DBS has marked effects on improvement of dystonic symptoms (Limousin et al., 1995; Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001; Coubes et al., 2004; Wichmann and Delong, 2006; Kringelbach et al., 2007; Ostrem and Starr, 2008; Vitek, 2008; Vidailhet et al., 2013). However, the exact mechanism of the effectiveness remains to be elucidated.
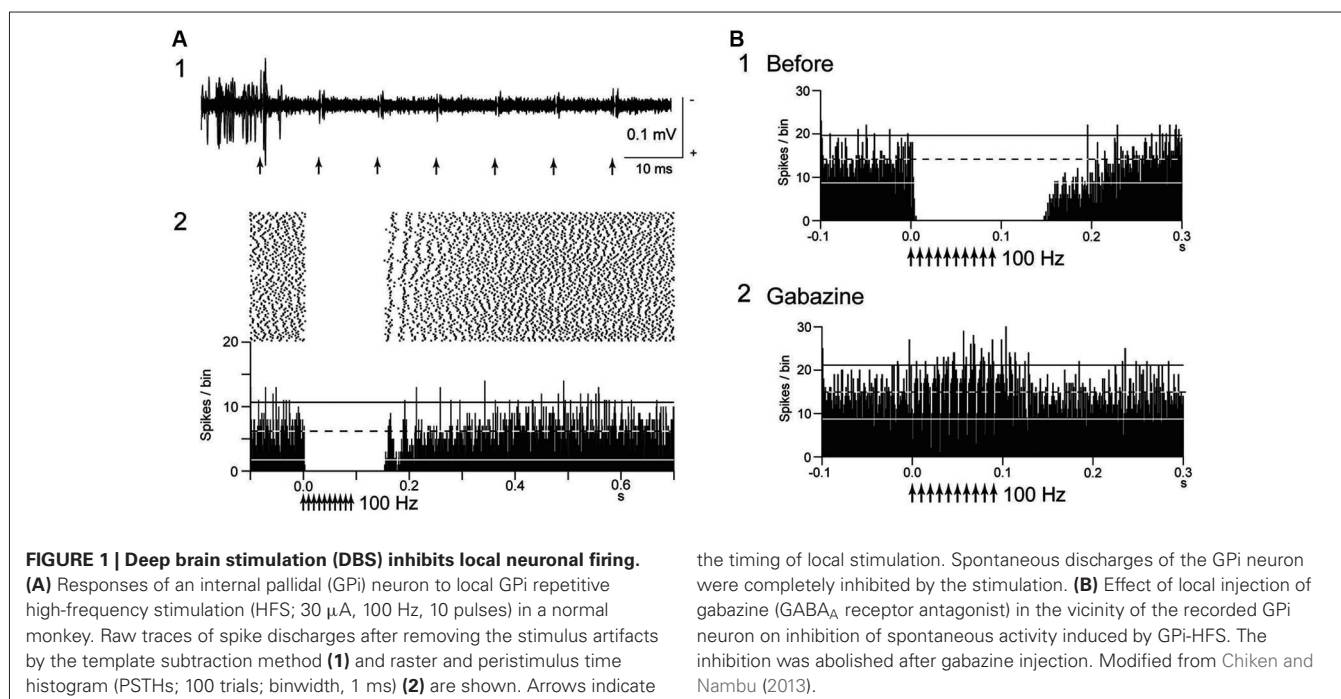
Since DBS gives rise to similar effects to those of lesions, it was originally considered to inhibit local neuronal elements. In fact, neuronal firings of neighboring neurons were inhibited by STN- or GPi-DBS (Boraud et al., 1996; Dostrovsky et al., 2000; Wu et al., 2001; Filali et al., 2004; Lafreniere-Roula et al., 2010). On the other hand, recent studies have emphasized activation of neuronal elements. Actually, STN-DBS increased activity of GPi neurons through the excitatory STN-GPi projections (Hashimoto et al., 2003; Galati et al., 2006; Reese et al., 2011), and GPi-DBS reduced activity of thalamic neurons through the inhibitory GPi-thalamic projections (Anderson et al., 2003; Pralong et al., 2003; Montgomery, 2006). In addition, recent studies reported multi-phasic responses consisting of excitation and inhibition in

GPi neurons during GPi-DBS (Bar-Gad et al., 2004; Erez et al., 2009; McCairn and Turner, 2009; Leblois et al., 2010). In this article, we critically review recent studies, and discuss the possible mechanism of effectiveness of DBS.

## DEEP BRAIN STIMULATION (DBS) INHIBITS LOCAL NEURONAL ELEMENTS

Both DBS and lesion were found to produce similar benefits on alleviation of symptoms. For example, STN-DBS has similar effects on Parkinsonian motor signs (Benazzouz et al., 1993; Benabid et al., 1994; Limousin et al., 1995) to the STN-lesion (Bergman et al., 1990; Aziz et al., 1991; Levy et al., 2001) and blockade of synaptic transmission from the STN to the GPi (Graham et al., 1990; Brotchie et al., 1991). Thus, DBS was originally assumed to inhibit local neuronal elements. Actually, the most common effect of STN- or GPi-HFS on neighboring neurons was reduction of the firing rates.

Distinct suppression of neuronal activity was recorded during STN-DBS around the stimulating sites in Parkinsonian patients during stereotactic surgery (Filali et al., 2004; Welter et al., 2004). Similar results were also obtained in animal models, such as Parkinsonian monkeys (Meissner et al., 2005; Moran et al., 2011) and rats (Tai et al., 2003; Shi et al., 2006). Stimulus artifacts hinder detection of spikes during 2–3 ms after stimulus pulses and some spikes may be obscured when neuronal activities are recorded nearby the stimulating electrodes. Recent studies enabled detection of spikes just after stimulus pulses by removal of stimulus artifacts using the template subtraction method (Wichmann, 2000; Hashimoto et al., 2002) and confirmed that STN-DBS decreased firing of neighboring neurons (Meissner et al., 2005; Moran et al., 2011). Although STN-HFS much decreased neuronal firing around the stimulation site, complete cessation of

**FIGURE 1 | Deep brain stimulation (DBS) inhibits local neuronal firing.**
**(A)** Responses of an internal pallidal (GPi) neuron to local GPi repetitive high-frequency stimulation (HFS; 30 μA, 100 Hz, 10 pulses) in a normal monkey. Raw traces of spike discharges after removing the stimulus artifacts by the template subtraction method **(1)** and raster and peristimulus time histogram (PSTHs; 100 trials; binwidth, 1 ms) **(2)** are shown. Arrows indicate the timing of local stimulation. Spontaneous discharges of the GPi neuron were completely inhibited by the stimulation. **(B)** Effect of local injection of gabazine (GABA$_A$ receptor antagonist) in the vicinity of the recorded GPi neuron on inhibition of spontaneous activity induced by GPi-HFS. The inhibition was abolished after gabazine injection. Modified from Chiken and Nambu (2013).

STN firing was observed in a limited number of neurons. STN-HFS at 140 Hz reduced mean firing rate of STN neurons by 77% in Parkinsonian patients, and among them, 71% of STN neurons exhibited residual neuronal activity, while only 29% of STN neurons exhibited total inhibition (Welter et al., 2004). Similar results were also observed in Parkinsonian monkeys (Meissner et al., 2005), and Parkinsonian and normal rats (Tai et al., 2003). Decreased abnormal oscillatory activity in the STN was also observed during STN-DBS in Parkinsonian monkeys (Meissner et al., 2005). Inhibitory effects sometimes outlasted the stimulus period (Tai et al., 2003; Filali et al., 2004; Welter et al., 2004).

Inhibitory effects of GPi-DBS on firing of the neighboring neurons were also reported (Boraud et al., 1996; Dostrovsky et al., 2000; Wu et al., 2001; McCairn and Turner, 2009). Complete inhibition of local neuronal firing was more commonly induced by GPi-DBS than by STN-DBS (**Figure 1A**). GPi-HFS at 100 Hz induced complete inhibition of 76% of neighboring neurons in normal monkeys (Chiken and Nambu, 2013), and the inhibition outlasted the stimulus period, sometimes over 100 ms after the end of stimulation. Similar post-train inhibition was also observed in Parkinsonian patients (Lafreniere-Roula et al., 2010).
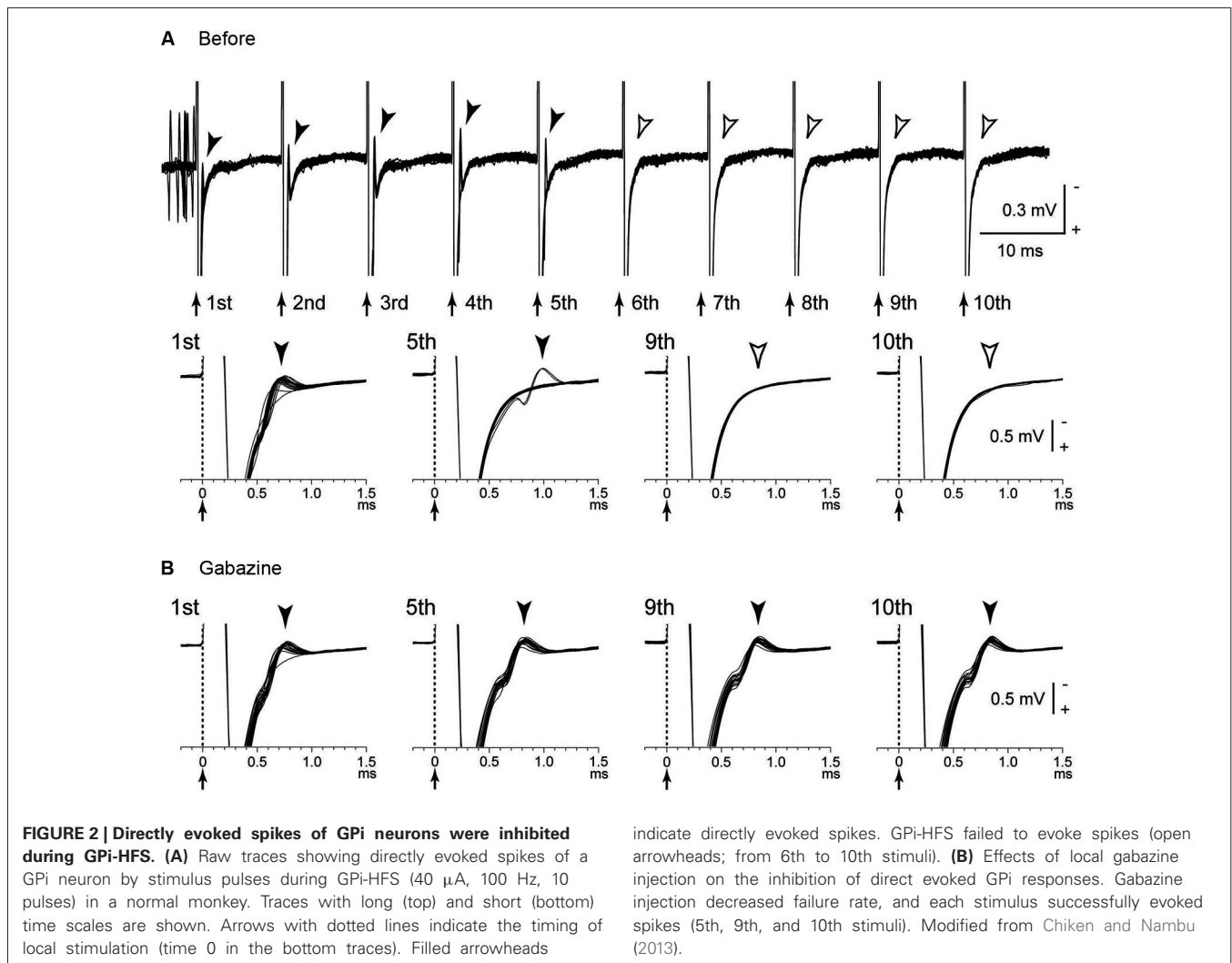
To the contrary, multiphasic responses consisting of the excitation and inhibition during GPi-HFS were recently observed in GPi neurons of Parkinsonian monkeys (Bar-Gad et al., 2004; Erez et al., 2009; McCairn and Turner, 2009) and dystonic hamsters (Leblois et al., 2010). The discrepant results may be due to differences in stimulus parameters used in these experiments: larger axons are easily activated by electrical stimulation than smaller ones (Ranck, 1975), and continuous repetitive stimulation might cause failure of postsynaptic events due to receptor desensitization and/or transmitter depletion (Wang and Kaczmarek, 1998; Zucker and Regehr, 2002). Such multiphasic responses may normalize abnormal firings, such as bursting and oscillatory activity in Parkinson's disease and dystonia as described below.

## MECHANISM OF INHIBITION

Several possible mechanisms account for the inhibitory responses have been proposed, including depolarization-block and inactivation of voltage-gated currents (Beurrier et al., 2001; Shin et al., 2007). However, these are less probable, because both single-pulse and low-frequency stimulation in the GPi evoked intense short latency inhibition in neighboring neurons (Dostrovsky et al., 2000; Dostrovsky and Lozano, 2002; Chiken and Nambu, 2013). Another possible mechanism is that the inhibition is caused by activation of GABAergic afferents in the stimulated nucleus (Boraud et al., 1996; Dostrovsky et al., 2000; Dostrovsky and Lozano, 2002; Meissner et al., 2005; Johnson et al., 2008; Liu et al., 2008; Deniau et al., 2010). A recent study confirmed that inhibitory responses induced by GPi-HFS were mediated by GABA$_A$ and GABA$_B$ receptors (Chiken and Nambu, 2013; **Figure 1B**). GABAergic inhibition is strong and inhibits even directly evoked spikes by GPi stimulation, which is characterized constant- and short latency (**Figures 2A, B**; Chiken and Nambu, 2013).

The GPi receives excitatory glutamatergic inputs from the STN as well as inhibitory GABAergic inputs from the striatum and GPe (Smith et al., 1994; Shink and Smith, 1995). Afferent axon terminals from the STN are also activated by the stimulation, but the glutamatergic excitation is probably overwhelmed because of predominance of GABAergic inputs in the GPi (Shink and Smith, 1995). On the other hand, many GPe neurons exhibited complex responses composed of both excitation and inhibition during GPe-HFS (Chiken and Nambu, 2013). The density of GPe terminals on GPi neurons is higher than those on GPe neurons

**FIGURE 2 | Directly evoked spikes of GPi neurons were inhibited during GPi-HFS. (A)** Raw traces showing directly evoked spikes of a GPi neuron by stimulus pulses during GPi-HFS (40 µA, 100 Hz, 10 pulses) in a normal monkey. Traces with long (top) and short (bottom) time scales are shown. Arrows with dotted lines indicate the timing of local stimulation (time 0 in the bottom traces). Filled arrowheads indicate directly evoked spikes. GPi-HFS failed to evoke spikes (open arrowheads; from 6th to 10th stimuli). **(B)** Effects of local gabazine injection on the inhibition of direct evoked GPi responses. Gabazine injection decreased failure rate, and each stimulus successfully evoked spikes (5th, 9th, and 10th stimuli). Modified from Chiken and Nambu (2013).
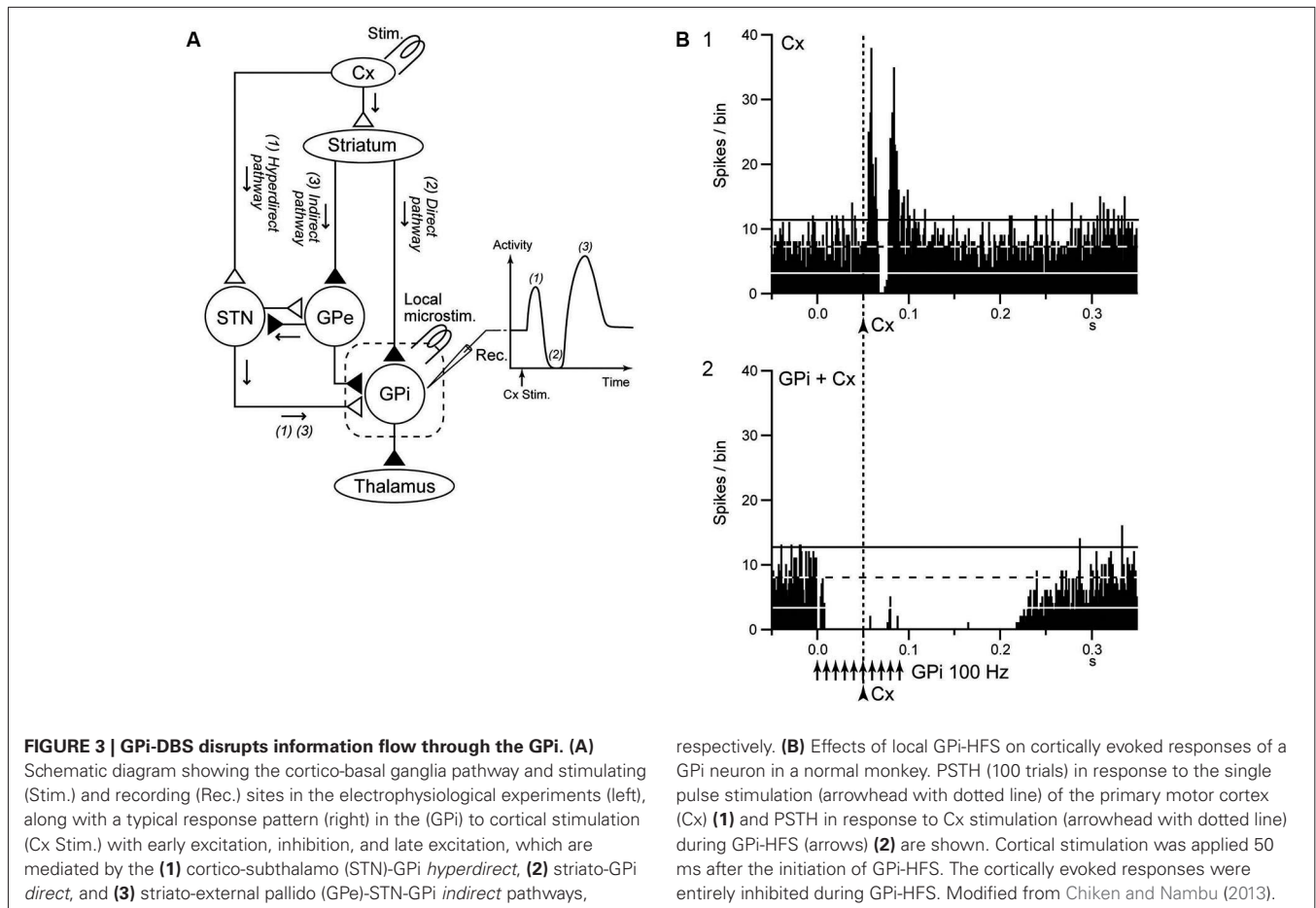
(Shink and Smith, 1995), and the balance between GABAergic and glutamatergic inputs may explain the different effects between GPe-HFS and GPi-HFS. Similarly, STN-HFS stimulated both glutamatergic and GABAergic afferents and generated both excitatory and inhibitory post-synaptic potentials (EPSPs and IPSPs) in the STN neurons (Lee et al., 2004). Thus, HFS activates afferent axons in the stimulated nucleus, and the effects vary depending on the composition of the inhibitory and excitatory axon terminals.

## DEEP BRAIN STIMULATION (DBS) EXCITES LOCAL NEURONAL ELEMENTS

It is rational that local stimulation excites local neuronal elements. Actually, directly evoked spikes, which are characterized by short- and constant latency, are induced in GPi neurons by GPi-HFS (Johnson and McIntyre, 2008; McCairn and Turner, 2009). Such excitation may propagate through efferent projections. Thalamic activity was reduced during GPi-HFS through inhibitory GPi-thalamic projections in Parkinsonian monkeys (Anderson et al., 2003) and dystonia patients (Pralong et al., 2003; Montgomery,

2006). GPi activity was increased during STN-DBS through excitatory STN-GPi projections (Hashimoto et al., 2003; Galati et al., 2006; Reese et al., 2011). STN-DBS increased both glutamate and GABA levels in the substantia nigra pars reticulata (SNr) of normal rats in microdialysis studies (Windels et al., 2000; see also Windels et al., 2005). An intraoperative microdialysis study revealed that STN-DBS produced significant increase in extracellular concentration of cyclic guanosine monophosphate (cGMP) in the GPi (Stefani et al., 2005). Functional magnetic resonance imaging (MRI) and positron emission tomography (PET) studies in humans indicated that efferent outputs from the stimulated nucleus are excited during DBS (Jech et al., 2001; Hershey et al., 2003; Boertien et al., 2011). Changes of the firing rates and patterns of target nuclei may normalize abnormal firings, such as bursting and oscillatory activity, which are observes in the cortico-basal ganglia loop of Parkinson's disease and dystonia (Anderson et al., 2003; Hashimoto et al., 2003; Hammond et al., 2007; Johnson et al., 2008; Vitek, 2008; Deniau et al., 2010).

According to the modeling study (McIntyre et al., 2004), sub-threshold HFS suppressed intrinsic firings in the cell bodies, while
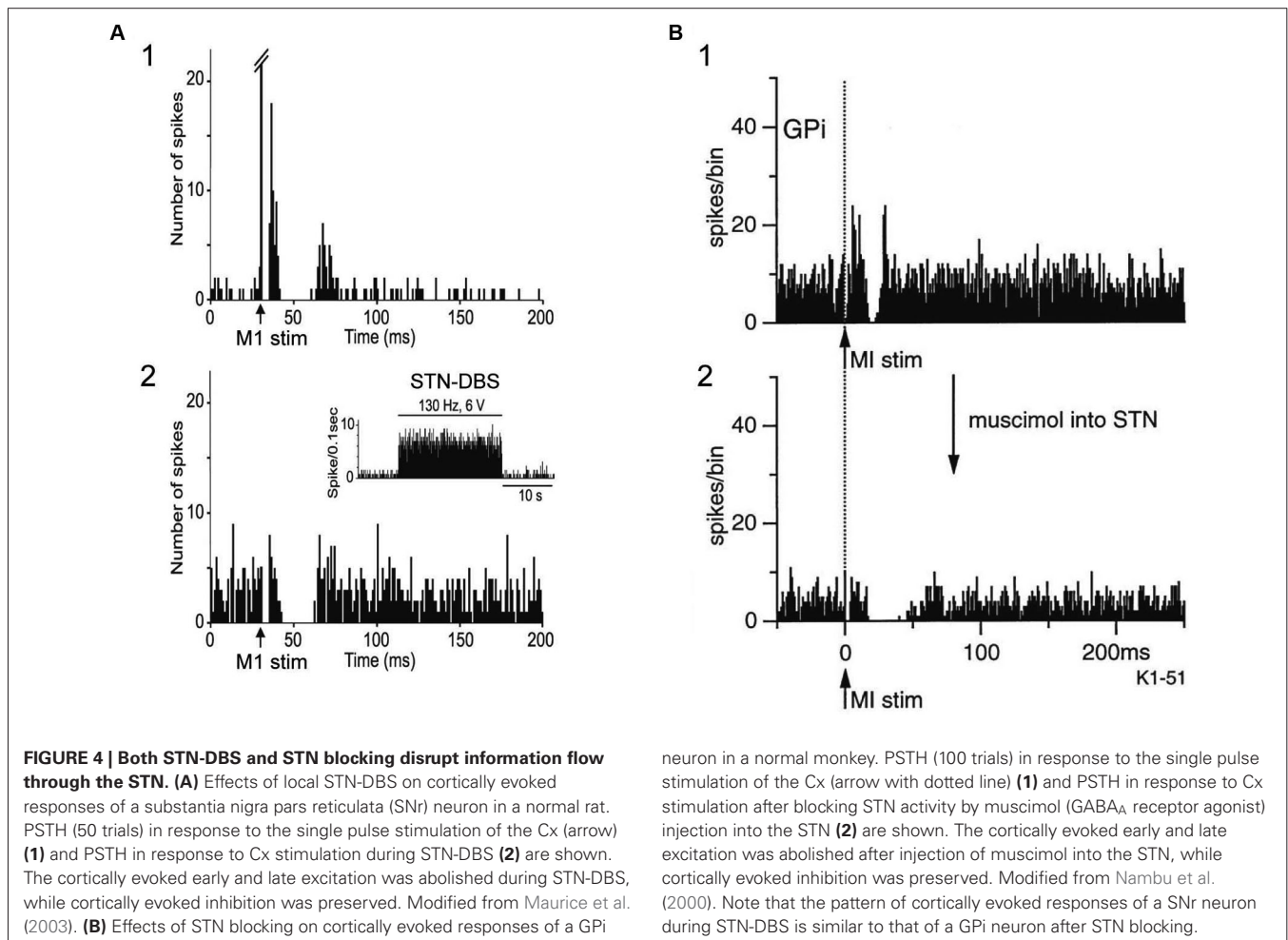
**FIGURE 3 | GPi-DBS disrupts information flow through the GPi. (A)** Schematic diagram showing the cortico-basal ganglia pathway and stimulating (Stim.) and recording (Rec.) sites in the electrophysiological experiments (left), along with a typical response pattern (right) in the (GPi) to cortical stimulation (Cx Stim.) with early excitation, inhibition, and late excitation, which are mediated by the **(1)** cortico-subthalamo (STN)-GPi *hyperdirect*, **(2)** striato-GPi *direct*, and **(3)** striato-external pallido (GPe)-STN-GPi *indirect* pathways,

respectively. **(B)** Effects of local GPi-HFS on cortically evoked responses of a GPi neuron in a normal monkey. PSTH (100 trials) in response to the single pulse stimulation (arrowhead with dotted line) of the primary motor cortex (Cx) **(1)** and PSTH in response to Cx stimulation (arrowhead with dotted line) during GPi-HFS (arrows) **(2)** are shown. Cortical stimulation was applied 50 ms after the initiation of GPi-HFS. The cortically evoked responses were entirely inhibited during GPi-HFS. Modified from Chiken and Nambu (2013).

suprathreshold HFS generated efferent outputs at the stimulus frequency in the axon without representative activation of the cell bodies. Thus, although stimulation may fail to activate cell bodies of GPi neurons due to strong GABAergic inhibition, it can still excite the efferent axons and provide inhibitory inputs to the thalamus at the stimulus frequency.

DBS also antidromically excites afferent axons. Actually, antidromic activation of GPi neurons induced by STN-DBS was observed in Parkinsonian monkeys (Moran et al., 2011), and antidromic activation of thatamic (Vop) neurons induced by GPi-DBS was observed in Parkinsonian patients (Montgomery, 2006). Low intensity STN-HFS induced GABAergic inhibition in the SNr through antidromic activation of GPe neurons projecting to both the STN and SNr (Maurice et al., 2003; see also Moran et al., 2011), whereas higher intensity stimulation induced glutamatergic excitation in the SNr through activation of STN-SNr projections. STN-HFS also activated motor cortical neurons antidromically and suppressed abnormal low frequency synchronization including beta band oscillation in Parkinsonian rats (Li et al., 2007, 2012; Degos et al., 2013). Recent development of optogenetics has enabled selective stimulation of afferent inputs or efferent outputs, and contribute to analyzing the mechanism of effectiveness of DBS. A recent study has shown that selective stimulation of cortico-STN afferent

axons can robustly ameliorate symptoms in Parkinsonian rats without activation of STN efferent axons (Gradinaru et al., 2009), suggesting that therapeutic effects of STN-DBS may be exclusively accounted for activation of cortico-STN afferent axons.

It is also probable that STN-DBS induces dopamine release through STN-SNc projections. STN-DBS induced dopamine release by activation of nigrostriatal dopaminergic neurons in rats (Meissner et al., 2003) and pigs (Shon et al., 2010), however it did not increase dopamine level of the striatum in human patients (Abosch et al., 2003; Hilker et al., 2003). DBS may also affect neurons whose axons pass nearby the stimulating site. A model-based study showed that clinically effective STN-DBS also activated the lenticular fasciculus, which is composed of GPi-thalamic fibers, in addition to STN neurons temselves (Miocinovic et al., 2006). Actually, STN-DBS induced direct excitation of GPi neurons through activation of the lenticular fasciculus (Moran et al., 2011).

Participation of non-neuronal glial tissues should also be considered as one of possible mechanisms of DBS effectiveness. DBS induced glutamate and adenosine triphosphate (ATP) release from astrocytes (Fellin et al., 2006; Tawfik et al., 2010). A recent study revealed that HFS applied to the thalamus induced abrupt increase in extracellular ATP and adenosine (Bekar et al., 2008).

**FIGURE 4 | Both STN-DBS and STN blocking disrupt information flow through the STN. (A)** Effects of local STN-DBS on cortically evoked responses of a substantia nigra pars reticulata (SNr) neuron in a normal rat. PSTH (50 trials) in response to the single pulse stimulation of the Cx (arrow) **(1)** and PSTH in response to Cx stimulation during STN-DBS **(2)** are shown. The cortically evoked early and late excitation was abolished during STN-DBS, while cortically evoked inhibition was preserved. Modified from Maurice et al. (2003). **(B)** Effects of STN blocking on cortically evoked responses of a GPi neuron in a normal monkey. PSTH (100 trials) in response to the single pulse stimulation of the Cx (arrow with dotted line) **(1)** and PSTH in response to Cx stimulation after blocking STN activity by muscimol (GABA$_A$ receptor agonist) injection into the STN **(2)** are shown. The cortically evoked early and late excitation was abolished after injection of muscimol into the STN, while cortically evoked inhibition was preserved. Modified from Nambu et al. (2000). Note that the pattern of cortically evoked responses of a SNr neuron during STN-DBS is similar to that of a GPi neuron after STN blocking.

Adenosine activation of A1 receptors depressed excitatory transmission in the thalamus, and alleviated tremor in a mouse model. Thus, it is possible that ATP and glutamate are released from astrocytes triggered by DBS and modulate neuronal activity in the stimulated nucleus (Vedam-Mai et al., 2012; Jantz and Watanabe, 2013).

## DEEP BRAIN STIMULATION (DBS) DISRUPTS NEURONAL TRANSMISSION

The striatum and STN are input stations of the basal ganglia and receive inputs from a wide area of the cerebral cortex (Mink, 1996; Nambu et al., 2002). The information is processed through the *hyperdirect*, *direct*, and *indirect* pathways and reaches the GPi/SNr, the output station of the basal ganglia (**Figure 3A**). During voluntary movements, neuronal signals originating in the cortex are considered to be transmitted through these pathways, reach the GPi/SNr and control movements (Mink, 1996; Nambu et al., 2002). Signal transmission through the *direct* pathway reduces GPi activity and facilitates movements by disinhibiting the thalamus, whereas the *hyperdirect* and *indirect* pathways increase GPi activity and suppress movements (Nambu et al., 2002; Nambu, 2007; Kravitz et al., 2010; Sano et al., 2013).

Chiken and Nambu (2013) recently examined responses of GPi neurons evoked by motor cortical stimulation during GPi-HFS in normal monkeys. In that study, both cortically evoked responses and spontaneous discharges were completely inhibited during GPi-HFS by strong GABAergic inhibition (**Figure 3B**), suggesting that GPi-HFS blocks information flow through the GPi. Since abnormal cortically evoked responses (Chiken et al., 2008; Kita and Kita, 2011; Nishibayashi et al., 2011) and abnormal bursts and oscillatory activity (Wichmann et al., 1994; Bergman et al., 1998; Starr et al., 2005; Brown, 2007; Chiken et al., 2008; Nishibayashi et al., 2011; Tachibana et al., 2011) were observed in GPi neurons in Parkinson's disease and dystonia, signal transmission of such abnormal activities to the thalamus and motor cortex would be responsible for motor symptoms. Thus, disruption of the abnormal information flow could suppress expression of motor symptoms. This mechanism may explain the paradox that GPi-DBS produces similar therapeutic effects to lesions of the GPi: both GPi-DBS and GPi-lesion interrupt abnormal information flow through the GPi.

STN-DBS may also interrupt neurotransmission of abnormal signals. Maurice et al. (2003) examined the effects of STN-DBS on cortically evoked responses of SNr neurons in normal rats.

**FIGURE 5 | Mechanism underling effectiveness of deep brain stimulation (DBS)**. DBS activates axon terminals in the stimulated nucleus and induces release of large amount of neurotransmitters, such as GABA and glutamate, and dissociates inputs and outputs in the stimulated nucleus, resulting in disruption of abnormal information flow through the cortico-basal ganglia loop.
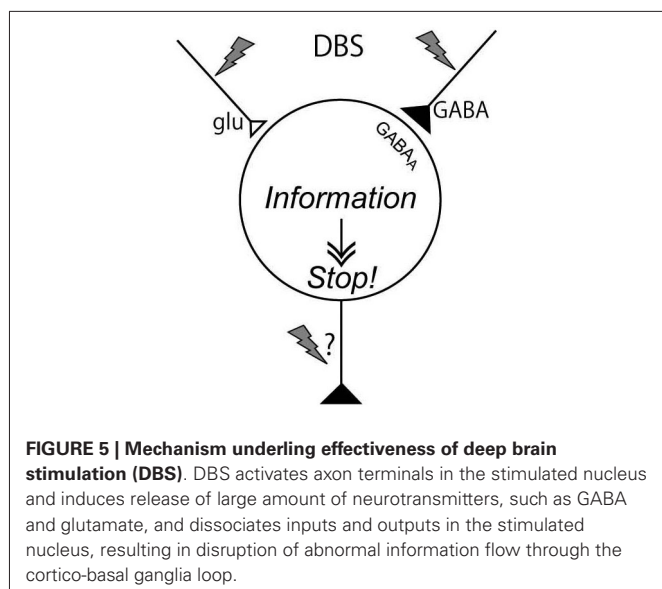
Cortically evoked early and late excitation was totally abolished during high intensity STN-HFS, and much reduced during low intensity STN-DBS, while cortically evoked inhibition was preserved (**Figure 4A**), suggesting that information flow through the trans-STN pathway was blocked by STN-DBS without interrupting other pathways. The response patterns of SNr neurons during STN-DBS are similar to those of GPi neurons during STN blockade by muscimol in normal monkeys (Nambu et al., 2000; **Figure 4B**). Thus it is rational that STN-DBS has similar effect to lesion or silencing of the STN. In Parkinson's disease, due to the loss of dopaminergic modulation, the information flow through the striato-GPi *direct* pathway is weakened, whereas the information flow through the striato-GPe *indirect* pathway is facilitated. Both STN-DBS and STN lesioning may alter the balance of inhibitory inputs through the *direct* pathway and excitatory inputs through the *hyperdirect* and *indirect* pathways to the GPi by disrupting information flow through the STN, and effectively alleviate bradykinesia seen in Parkinson's disease. Similar idea, a functional disconnection of the stimulated elements, has also proposed by other groups (Anderson et al., 2006; Deniau et al., 2010; Moran et al., 2011).

## CONCLUSION

DBS has variety of effects on neurons in the stimulated nucleus of the cortico-basal ganglia loop, though transmitter release, orthodromic activation of efferent axons, antidromic activation of afferent axons, and direct stimulation of passing axons nearby the stimulating electrode. The effects vary depending on the neural composition of the stimulated nucleus, and the effects extend much wider than originally expected. However, a common mechanism would underlie the effectiveness of DBS: DBS dissociates inputs and outputs in the stimulated nucleus and disrupts abnormal information flow through the cortico-basal ganglia loop (**Figure 5**). The mechanism may explain the paradox that

DBS produces similar therapeutic effects to lesions or silencing of the nucleus.

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