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Reviews

Latest View on the Mechanism of Action of Deep Brain Stimulation

Constance Hammond, PhD,^{1*} Rachida Ammari,^{1,2} Bernard Bioulac, MD, PhD,² Liliana Garcia, PhD²

¹Institut de Neurobiologie de la Méditerranée (INMED, U901), Unité mixte Inserm-Université Aix Marseille II,

Marseille Cédex 9, France

²UMR 5227 CNRS-Université Bordeaux 2, Bordeaux Cédex, France

Abstract: How does deep brain stimulation (DBS) applied at high frequency (100 Hz and above, HFS) in diverse points of cortico-basal ganglia thalamo-cortical loops alleviate symptoms of neurological disorders such as Parkinson's disease, dystonia, and obsessive compulsive disorders? Do the effects of HFS stem solely or even largely from local effects on the stimulated brain structure or are they also mediated by actions of HFS on distal structures? Indeed, HFS as an extracellular stimulation is expected to activate subsets of both afferent and efferent axons, leading to antidromic spikes that collide with ongoing spontaneous ones and orthodromic spikes that evoke synaptic responses in target neurons. The present review sug-

Deep brain stimulation at high frequency (HFS) has the potential to provide substantial benefit for various neurologic and neuropsychiatric diseases. HFS is an intracerebral, extracellular stimulation consisting of short pulses (in the order of 100 μ s) regularly applied at a frequency of at least 100 Hz over a period of several years. First observed to alleviate tremor in ventral thalamus and pallidum,¹ HFS is now widely used in ventral thalamus for essential tremor,² in the internal pallidal segment (GPi) or subthalamic nucleus (STN) for Parkinson's disease (PD),^{3–5} in the GPi for generalized dystonia,^{6,7} and more recently for other diseases such as treatment-resistant obsessive com-

gests that HFS interfere with spontaneous pathological patterns by introducing a regular activity in several nodal points of the network. Therefore, the best site of implantation of the HFS electrode may be in a region where the HFS-driven activity spreads to most of the identified, dysrhythmic, neuronal populations without causing additional side effects. This should help tackling the most difficult issue namely, how does the regular HFS-driven activity that dampens the spontaneous pathological one, restore neuronal processing along cortico-basal gangliathalamo-cortical loops? © 2008 Movement Disorder Society

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pulsive disorder (OCD),^{8,9} Tourette syndrome,^{10,11} and depression.¹² Sites of stimulation are located inside the cortico-basal ganglia-thalamo-cortical loops, in motor or limbic regions, depending on the clinical signs.

Two major and nonexclusive explanations have been proposed for the effect of HFS: (1) it silences stimulated neurons and (2) it introduces a new activity in the network. The first theory stems from the observation that, functionally, HFS produces the same effect as a lesion of the stimulated area. The second hypothesis proposes that HFS injects in a point of the circuit a HFS-driven activity that propagates and consequently modifies the pathological spontaneous activity in many nuclei. The clarification of the mechanisms of action of HFS is imperative to avoid implanting electrodes in regions having a low impact on clinical signs and/or leading to activation of undesirable regions and incapacitating side effects. In this review, we focus on results obtained within the last 4 years from multiunit and single cell electrophysiological recordings.

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Dr. Constance Hammond, INMED Inserm, 163 route de Luminy, BP13, 13273 Marseille Cédex 9, France.

E-mail: hammond@inmed.univ-mrs.fr

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MECHANISMS OF STN-HFS IN THE CASE OF PARKINSON'S DISEASE

Increased synchronization and the appearance of pathological oscillations in the activity patterns of populations of STN and GP neurons but also in motor cortical networks are salient aspects of Parkinsonism. Pathological synchronization has been observed in human PD patients,¹³ 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys¹⁴ and rodents with 6-hydroxy-dopamine (6-OHDA) lesions,¹⁵ suggesting functional alterations in the basal ganglia network. In particular, increased coherence in the β -band (13–30 Hz) is correlated with the severity of symptoms in humans.^{16–18}

Mechanisms of STN-HFS have long been reduced to a lesion-like or inhibition hypothesis until biochemical, metabolic, and electrophysiological data in experimental models and patients together with modeling studies^{19–23} provided consistent evidence in favor of an activation.

Basal ganglia are made up of different neuronal populations scattered in five different nuclei (see Fig. 1): caudate and putamen (striatum in rodents), globus pallidus (external and internal), subthalamic nucleus (STN), and substantia nigra pars reticulata (SNr) and



FIG. 1. STN and the basal ganglia network STN-HFS preferentially activates axons thus generating spikes that propagate in the antidromic (toward STN, motor cortex, GPe and PPN somas) and orthodromic (toward GPe, GPi, SNr, SNc, PPN) directions. Passing fibers can also be activated. As a result, basal ganglia nuclei such as SN and GP together with motor cortical areas are directly affected by STN-HFS. The striatum is mainly indirectly affected via the modulation of dopaminergic SNc neurons and cortical afferents. When antidromic spikes propagate back to a structure, they may invade somas and axon collaterals and thus activate other projection neurons and local interneurons when they exist. Insets show simplified cortical²⁴ (top) and GPe (bottom) networks. \blacksquare , neuronal populations directly affected by STN-DBS; \rightarrow , antidromic activation of axons, \Rightarrow , orthodromic activation of axons; \leftarrow , GABAergic neuron; \simeq , glutamatergic neuron.

compacta (SNc). The degeneration of the dopaminergic neurons of the SNc and the consequent loss of dopamine in the striatum leads to "typical" PD. STN neurons occupy a strategic position as they are the only glutamatergic neurons of the basal ganglia network, receive afferents from motor-related cortical areas, project to all nuclei of the basal ganglia (though to a lesser extent to striatum), and are reciprocally connected with GPe and brainstem neurons of the pedunculopontine nucleus (PPN).²⁵ Therefore, STN stimulation may activate diverse pathways and have widespread effects.

Preparations, Parameters of Stimulation, and Excitation of Neural Elements

Different types of preparations have been used to study HFS mechanisms from anesthetized in vivo models of PD to in vitro slices. Recordings have been performed in patients as well. Each preparation has its own advantages and pitfalls, but their combination should allow understanding HFS mechanisms as long as we are aware of the limitations of the technique used. In this review, HFS refers to high frequency stimulations in vivo and in vitro.

The question of the mechanisms of action of HFS relies on the analysis of what does a high frequency and long duration stimulation of neuronal elements (HFS is applied for years). Electrophysiologists are used to study potential changes in response to single stimulations but here the question is far more complex mainly for technical reasons as recordings have to be maintained for minutes or hours and spikes identified among artifacts. If all studies on HFS mechanisms test high frequency (100-180 Hz) stimuli, they rarely apply them for long durations. Considering synaptic plasticity (potentiation or depression) that usually occurs in synaptic transmission after tetanic stimulation,²⁶ ultrashort (ms, s) and long (days, years) duration stimulations could evoke very different responses. Even though some of the symptoms are immediately improved,²⁷ when describing the electrophysiological effects of STN-HFS one must keep in mind whether it is a shortor a long-term effect. To compare results from different studies, intensity of stimulation is not as informative as charge density (µC/cm²/phase).²⁸ This parameter depends on the diameter of the stimulation electrode or contact and is not always available from papers. For this reason, the value of current intensity is not mentioned. All protocols use short pulses (60-200 us) of stimulation. Since cell bodies and axons have different chronaxies (chronaxy is the shortest duration of an effective electrical stimulus having a strength equal to twice the minimum strength required for excitation), this value is used to determine which neural elements are excited by HFS. Cell bodies have chronaxies in the 1- to 10-ms range, large myelinated fibers have chronaxies in the 30- to 200- μ s range, and small myelinated fibers have chronaxies in the 200- to 700- μ s range.²⁹ For example, chronaxies for tremor reduction by HFS were estimated to be ~65 μ s for thalamic and around 75 μ s for pallidal stimulation,³⁰ suggesting that HFS targets large myelinated axons.

Is STN-HFS Noxious to STN Neurons?

Before analyzing the electrophysiological effect of STN-HFS, the first point to verify is the extent of STN lesion due to the chronic presence of the electrode and chronic application of HF stimulation. The classical Medtronic electrode was implanted in one STN in control or MPTP-treated monkeys, and the stimulation continuously applied for 7 months (pulses at 130 Hz, 60-µs duration). Cell counts performed in Nissl-stained coronal sections of the STN showed that the STN having the implant had only 5% difference in total cell number when compared with the side that did not have the implant.³¹ Therefore, the chronically implanted electrode does not induce local degenerescence and the beneficial effects of STN-HFS are not mediated by a lesion of the STN as already suggested by human postmortem studies, which indicate little tissue damage associated with chronic HFS.³²

Does STN-HFS Lock the Electrophysiological Activity of STN Neurons to Harmonics of the Stimulation Frequency?

Studies of the effect of STN-HFS locally on STN neurons gave the most controversial data. This probably results from the difficulty to separate the very short latency evoked spikes from the stimulation artifacts or as we will see later on the difference between cell body and axonal activity in some conditions. Benazzouz's group recorded inhibition of STN neurons during STN-HFS in 6-OHDA rats³³ but recently described that this inhibition only lasted 4 ms after each stimulus when the interval between two stimuli was fixed at 7.7 ms (130 Hz).³⁴ In patients, STN-HFS of short durations decreased STN neurons activity³⁵ and changed the firing pattern of some STN neurons.³⁶ Mechanisms underlying these observations have not been identified.

In slices, STN activity is very low when compared with that in vivo and does not show the pathological alterations resulting from dopamine depletion probably because the basal ganglia network is absent in coronal slices. Slices have however the advantage of allowing intracellular recordings and precise analysis of the correspondence between stimuli and spikes. In our experiments, STN spontaneous spikes disappeared during STN-HFS and were replaced by spikes evoked by and locked to stimuli (Fig. 2A). The STN firing pattern under HFS consisted of trains of evoked spikes in the γ -range frequency.^{22,40} Interestingly, the fixed latency of HFS-driven spikes (close to 0 ms), the presence of the initial segment-somatodendritic (IS-SD) break in some of the recordings (Fig. 2A right), and the lack of effect of blockers of synaptic transmission, all strongly suggested that HFS directly activated the STN neuronal membrane at the level of their cell body, initial segment or first Ranvier node (Fig. 1A, inset STN). HFS-evoked spikes by colliding with orthodromic, spontaneous ones that had a lower frequency in slices, suppressed STN spontaneous activity in the activated STN neurons. Once HFS is turned off, STN neurons become silent during several seconds for two reasons: they are no longer excited by the electrical stimuli and their intrinsic voltage-dependent currents, in particular the persistent Na⁺ current, are blocked.⁴¹ Then, after a variable delay, this blockade resumes and the STN neuronal membrane can again autogenerate spikes and display its characteristic pacemaker activity.

One possible explanation for the controversial results obtained in vivo and in vitro is that action potentials evoked in axons by local HFS, inefficiently invade cell bodies in the antidromic direction due to geometric ratio. HFS would therefore lead to active axons and silent somas.^{42,43} Since extracellular microelectrode recordings are biased toward recording action potentials from cell bodies rather than axons, this would result in the appearance of decreased activity within the stimulated structure though efferent axons are excited (see discussion in Ref. 39). In contrast, intracellular or juxtacellular recordings record axonal spikes evoked at the level of the initial segment (IS spikes, Fig. 2A middle) and higher intensities of stimulation would compensate for the geometric ratio.

Does STN-HFS Antidromically Activate Afferent Neurons to the STN?

A stimulation applied in a nucleus may activate afferent axons and give rise to antidromically propagating spikes. Antidromic propagation refers to the propagation of axonal spikes from their point of initiation close to the stimulating electrode, toward cell bodies, i.e., in the direction opposite to physiological spikes that propagate in the orthodromic direction toward



FIG. 2. HFS-driven antidromic spikes. (A) Local activation of STN neurons in response to STN-HFS (note IS spike at t = 120 ms, middle and IS-SD break, right) (Garcia et al., unpublished figure) and antidromic invasion of (B) motor cortical neurons in response to STN-HFS (arrow head indicates collision, right),³⁷ (C) GPe neurons in response to STN-HFS (Ammari et al., unpublished data), (D) SNr neurons in response to STN-HFS (note collision, bottom trace, right),³⁸ and (E) Vop thalamic neurons in response to GPi-HFS (poststimulus raster plot, top, histogram, bottom, antidromic spikes, right).³⁹

axon terminals. STN-HFS thus evokes antidromic spikes in cortico-STN and GP-STN axons (see Fig. 1). But antidromic excitation of cortical and GP neurons may not be very efficient. For example, whereas the fast conducting branches in the highly myelinated brainstem region follow HFS, the slower conducting fibers in the poorly myelinated thalamic region fail to transmit consecutive antidromic spikes and maintain a steady low-frequency (6–12 Hz) spike output during the stimulation. $^{\rm 43}$

Because of this low probability of antidromic invasion of somas, antidromic spikes are usually evoked in a subset of afferent neurons only. So, a subset of layer V/VI neurons of motor cortex that project to STN⁴⁴ displayed antidromic spikes (latency around 2 ms) whose frequency decreased with time to a steady state



FIG. 3. HFS-driven orthodromic responses. Orthodromic responses of (A) GPi neurons in response to STN-HFS (complex sequence of excitation-inhibition-excitation),²³ (B) Vop thalamic neurons in response to GPi-HFS (antidromic activation followed by a complex sequence of excitation-inhibition-excitation, poststimulus raster, top, and histogram, bottom).³⁹

at around 40 Hz in response to 120 Hz STN stimulation³⁷ (Fig. 2B). Recordings of short latency evoked potentials over the motor cortex during STN-HFS also indicated that cortico-STN axons were most likely activated.⁴⁵ As glutamatergic cortico-STN neurons give off many axon collaterals in deep and superficial layers⁴⁶ that contact other projection neurons and local GABAergic interneurons, antidromic invasion of a subset of neurons may retrogradely affect cortical circuits in complex ways (Fig. 1, inset cortex).⁴⁷

STN-HFS in slices (130 Hz, 90 μ s) evoked antidromic spikes in a subset of GPe neurons with a mean latency of around 2 ms (Fig. 2C) that collided with the ongoing activity in the recorded neurons. If antidromic spikes propagate in the complex network of local GABAergic collaterals that synapse onto other GP neurons, this may have consequences on the activity of neighboring GP neurons⁴⁸ (Fig. 1, inset GP).

STN-HFS also activates axons passing through and near the STN. Thus short STN-HFS (130 Hz, 60 μ s, 30 s trains) in control rats in vivo antidromically activated a subpopulation of SNr neurons with a latency of around 1 ms,³⁸ probably as a result of the activation of ascending SNr axons. This decreased the spontaneous activity of the antidromically activated SNr neurons and inhibited other SNr neurons as shown in recordings³⁸ probably via the activation of the complex network of intranigral collaterals between GABAergic SNr cells.⁴⁹

In conclusion, STN-HFS antidromically activates subsets of neurons in the different nuclei that send axons to or close to the stimulated site. In that context, STN-HFS probably also antidromically activates PPN neurons that project to STN.^{50,51} Once evoked, antidromic axonal spikes propagate to their corresponding cell bodies at the stimulation frequency or its subharmonics. They may also propagate in recurrent axonal collaterals and activate synaptic transmission that impinges onto other projection neurons (GP, SNr) or local interneurons (see Fig. 1, insets cortex and GPe). The overall result on a network needs to know the probability of propagation of antidromic spikes in axonal branches⁴⁷ and how these spikes evoke synaptic responses at a long term.

Does STN-HFS Orthodromically Activate Target Neurons of the STN?

From their point of initiation, axonal spikes also propagate in the orthodromic direction toward axon terminals, i.e., along STN efferent axons (see Fig. 1). Do these spikes evoke postsynaptic responses? STN-HFS parameters that improved spontaneous movements and muscle tone (130, 210 µs, 25 s-5 min) in MPTP-treated monkeys evoked stimulus-locked double excitatory responses at latencies around 4 and 6 ms in the globus pallidus (GPe and GPi)²³ (Fig. 3A). It thus shifted the firing pattern of GPe and GPi neurons from irregular to stimulus-synchronized. The most probable mechanism underlying the earlier excitation is the orthodromic activation of STN efferent axons projecting to GP, the release of glutamate and the monosynaptic excitation of postsynaptic GPe or GPi neurons. In contrast, in control monkeys, bursts of 100 Hz stimuli (10 pulses) induced powerful excitatory responses in the GPe but inhibition in the GPi attributed to the activation of the disynaptic STN-GPe-GPi pathway.⁵²

Does STN-HFS similarly affect GP and SNr neurons? Deniau's group studied the spontaneous and evoked SNr activity before and during STN-HFS in control rats or rats treated with neuroleptics to block dopaminergic transmission. In control rats, STN-HFS (130 Hz, 60μ s, 30 s) evoked antidromic spikes and

inhibition as previously seen but also orthodromic spikes (excitation) in SNr neurons.³⁸ The short latency excitation is likely to result from the orthodromic activation of the excitatory STN-SNr glutamatergic axon terminals. In cataleptic rats, at parameters that reversed the catalepsy (130 Hz, 60-80 µs), STN-HFS regularized the pattern of discharge of SNr neurons as it significantly decreased the number of neurons exhibiting burst discharges and reduced the number of bursts emitted by bursting neurons.⁶³ In PD patients under surgical procedure, at parameters (130 Hz, 60 µs) that induce clinical improvement of rigidity and finger tapping, STN-HFS increased mean spike frequency of SNr neurons and evoked short latency (4 ms) excitatory responses. Autocorrelograms demonstrated the presence of a periodic spiking at 130 Hz. In parallel, the firing pattern changed from irregular to a "grouped" pattern consisting of groups of spikes separated by longer periods of pauses.⁵³ In another study in patients, STN-HFS (140 Hz, 60 µs) evoked in SNr neurons a three-phase sequence, inhibition (0-2 ms)-excitation (2-4 ms)-inhibition (4-7 ms)after the stimulation pulse. There was a 51% decrease in the percentage of the spikes contributing to bursts and a 70% decrease in the mean duration of bursting mode activity.⁵⁴

Therefore, STN-HFS in some GP and SNr neurons replaces the "pathological" activity encoded by the basal ganglia during PD by a stimulus-driven firing pattern. This new activity would result, at least in part, from the activation of STN efferent fibers. The multiphasic pattern of the responses (alternated periods of excitation and inhibition) suggests a participation of polysynaptic responses. This has to be confirmed since HFS usually suppresses polysynaptic responses. At present, the mechanisms underlying the complex responses recorded in the target neurons of the STN in response to short-term STN-HFS or GP-HFS are not yet elucidated.

Does STN-HFS Protect the Remaining SNc Neurons and Amplify Levodopa Treatment?

The protection from degeneration of the remaining dopaminergic neurons by STN-HFS has been investigated in murine and primate models of PD. Temel et al.⁵⁵ injected 6-OHDA at four sites in both striatum of rats. During the phase of ongoing neurodegeneration in the SNc, half of the lesioned rats were treated with bilateral STN-HFS (pulse width at 60 μ s, frequency at 130 Hz, 1 hour per day over a period of 3 months). This amount of STN modulation was suffi-

cient to obtain a significant rescue of SNc dopaminergic neurons from cell death. Bilateral STN-HFS not only had a protective effect on the number of TH positive neurons but also on the total number of neurons in the SNc. It could be argued that this effect resulted from a nonidentical retrograde degeneration of SNc dopaminergic neurons in the different lesioned rats and thus did not result from STN-HFS. For this reason, to mimic the clinical situation and to be able to observe neuroprotection, Benabid's group performed a subacute model of MPTP treatment in primates and induced a symmetrical 50% reduction of Nissl-stained and TH positive cells in the two SNc. They applied a unilateral STN-HFS after MPTP treatment and compared the number of Nissl-stained and TH-positive SNc cells between each side of the brain in two animals, the non-HFS side serving as a control. They found around 20% more dopaminergic neurons in the SNc of the side that underwent HFS when compared with the non-HFS side. When the HFS electrode was located outside the STN, the difference between both sides was not significant.³¹ Therefore STN-HFS may have offered neuroprotection to nigral dopaminergic neurons that would have degenerated as part of the disease process.

Several studies reported an excellent clinical outcome of STN-HFS in levodopa (L-dopa) responsive forms of Parkinson's disease,56 and STN-HFS allows the discontinuation of L-dopa or equivalent treatment or large reductions in daily dose⁵⁷ in contrast to GPi-HFS. The question therefore aroused whether STN-HFS favors dopamine release in the striatum. Savasta's group tested this hypothesis by measuring the extracellular content of dopamine with HPLC and its metabolites in the striatum of rats that underwent a partial 6-OHDA lesion of one SNc.⁵⁸ After a delay of 3 weeks to allow the degeneration of 70% of dopaminergic nigrostriatal fibers in the dorsolateral part of the striatum, they implanted the stimulation electrode in the STN and the microdialysis probe in the striatum, both ipsilateral to the lesion. The i.p. injection of L-dopa (50 mg/kg) increased by around three times the content of extracellular dopamine in the lesioned striatum measured 1 hour after the injection. STN-HFS at clinical parameters (130 Hz, 60 µs, during 1 hour) amplified by around 100% this L-dopa-induced increase of dopamine during the stimulation period and for the following 2.5-hour after the end of stimulation. In contrast, in intact animals, L-dopa failed to enhance the extracellular dopamine levels during the stimulation period. This suggests that STN-HFS interacts in a synergistic manner with L-dopa but the underlying mechanisms have not been elucidated. A simple explanation would be that STN-HFS acts by directly modulating the firing rate of the remaining dopaminergic neurones.^{59,60}

Which of the STN-HFS-Induced Electrophysiological Effects Are Related to Clinical Efficacy?

Ideally, to test this question, we should specifically block one by one the identified responses to HFS and analyze the consequences on motor behavior. This experiment is difficult to perform. We will propose some hypotheses as follows: a therapeutic electrophysiological effect is likely to (i) reduce pathological patterns in the basal ganglia, (ii) be recorded from output nuclei of the basal ganglia whichever site of the cortico-basal ganglia-thalamo-cortical loops is stimulated (in the same animal models), and (iii) allow re-establishment of a control response of output GPi and SNr neurons to cortical stimulation (triphasic response).

We have seen that HFS introduces a stimulationlocked, complex activity in subsets of neurons from many sites of the basal ganglia network (STN, motor cortex, GPe, GPi, SNr), and thus decreases ongoing pathological activity in these neurons. This may also be valid for PPN and the good results obtained on axial motor signs with STN-HFS in association with PPN-HFS⁶¹ may result from a change of PPN discharge pattern. Direct activation of passing fibers dorsal to the STN and in particular nigro-striatal and pallido-thalamic axons may also participate to the beneficial effect as the best position of the HFS electrode active contact is in the dorsal part of the STN.

To answer the second hypothesis, we can take the example of GPi-HFS and STN-HFS that both ameliorate clinical signs of PD. Do they have similar electrophysiological effects on GPi neurons in the primate model of PD? Bar-Gad et al.⁶² recorded the activity of GPi neurons in MPTP-treated monkeys in response to microstimulations applied in GPi (135 Hz, 200 µs, 600-3000 trains of 10 stimuli separated by 500 ms). They reported a double excitation with latencies of 3 and 6 ms, separated by a short period of inhibition. Overall 70% of the GPi neurons displayed a locked activity, i.e., they lost their basic firing pattern and switched to a predicted, orderly discharge that was locked to the stimulus. These results show striking similarities with those recorded in GPi with STN-HFS in MPTP-treated monkeys²³ (see earlier).

The third point was shown in SNr where STN-HFS reversed to control the classical triphasic response to

motor cortex stimulation⁶³ but the mechanisms have not been elucidated.

HFS FOR OTHER NEUROLOGICAL DISORDERS

HFS in Motor Cortico-Basal Ganglia-Thalamocortical Loop for Essential Tremor

HFS of ventral nuclei of the thalamus can dramatically relieve essential tremor in the majority of patients.^{2,64} Essential tremor is thought to arise from dysfunction of the glutamatergic olivocerebellar pathway, which projects to ventral thalamic (VL) nuclei.65 VL-HFS in rat brain slices silenced or suppressed the activity of thalamic relay neurons after a transient period of intense depolarization.⁶⁶ The authors hypothesized that VL-HFS introduced a functional deafferentation of stimulated neurons, thereby stopping tremor from propagating to thalamo-cortical loops. To test whether this depression of afferent synaptic transmission is selective, they stimulated at 5 Hz in two different loci within the VL to mimic afferent stimuli at tremor frequency. Both stimulations evoked excitatory postsynaptic potentials at 5 Hz in the recorded VL neuron. A concomitant short-duration HFS (125 Hz, for 10 s) in one locus or totally suppressed the 5 Hz EPSPs in the HFS-stimulated pathway but not in the nonstimulated one, suggesting that HFS selectively disrupts afferent synaptic transmission.⁶⁷ One of the underlying mechanisms could include the depression of excitatory glutamatergic transmission in the ventral thalamus by activation of the presynaptic A1 receptors. HFS releases ATP, the precursor of adenosine and local adenosine infusion suppresses tremor in the harmaline-treated mice.⁶⁸ However, these mechanisms have been identified during very short-term HFS (10 seconds) and may not sustain the long-term beneficial effects of VL-HFS.

HFS in Motor Cortico-Basal Ganglia-Thalamocortical Loop for Dystonia

Neuronal activity is altered in basal ganglia and ventral thalamic nuclei in dystonia.⁶⁹ The firing pattern of GPi neurons known to be regular in monkeys⁷⁰ consists in patients of irregular grouped discharges with intermittent pauses and a third of the neurons discharge at the frequency of the electromyogram.^{71,72} Neurons in ventral oralis posterior/intermediate nuclei of the thalamus (Vop/Vim) have a sustained activity at 130 to 150 Hz, organized in bursts lasting from 500 ms to 5 seconds and recurring at a frequency similar to that of dystonia frequency.⁷¹ GPi-HFS is currently used for primary generalized DYT-1 positive dystonia and idiopathic cervical dystonia.^{7,73,74} In contrast to Parkinson's disease, the beneficial effects of HFS in dystonia are not immediate but progressive over weeks to months. However, recordings in patients can only be performed during the surgical procedure, i.e. at t_0 , or in control animals, owing to the lack of reliable animal models of dystonia.

During short duration GPi-HFS, 50 to 70% of Vop neurons of the thalamus reduced their average discharge frequency with a delay of a few milliseconds in control monkeys⁷⁵ or dystonic patients,³⁹ suggesting that HFS activates GPi efferent axons that are GABAergic and inhibitory onto thalamic neurons (Fig. 3B). Moreover, 88% of Vop neurons were antidromically activated with 1-ms latency probably as a result of the activation of axons originating in Vop and passing in the vicinity of the GPi-HFS electrode (Fig. 2E).

HFS in Limbic Cortico-Basal Ganglia-Thalamocortical Loop for Obsessive Compulsive Disorder

Obsessive compulsive disorder has been consistently associated with metabolic hyperactivity in the caudate nucleus, medial thalamus, and orbitofrontal cortex in patients at rest.^{76–78} Recently, a dramatic increase in neuronal activity of the ventral caudate nucleus was identified and correlated to the patients' self-evaluated obsessions.⁷⁹ HFS of the ventral anterior internal capsule,⁸⁰ accumbens,⁸ or limbic STN⁸¹ are therapeutic approaches for treatment-resistant OCD. HFS mechanisms were studied with imaging techniques in patients and electrophysiological techniques in control rats as robust animal models of OCD are lacking.

HFS of the accumbens (130 Hz, 200 μ s, during 30 min) in control rats induced the inhibition of nearly all the recorded orbitofrontal neurons probably as a result of the antidromic activation of cortico-accumbens axons and other corticofugal axons.²⁴ The authors suggest that antidromic spikes propagate in axonal collaterals of cortical neurons and thus evoke inhibitory responses in neighboring neurons via GABAergic interneurons (Fig. 1, inset cortex). But this still has to be demonstrated as antidromic axonal spikes often inefficiently invade axon collaterals and somas.⁴³

CONCLUSION

The studies explained so far have focused on the effects of STN-HFS at the site of stimulation or of the first order neurons immediately downstream (orthodromic effect) or upstream (antidromic effects) the STN and in resting conditions. This last point is of importance since results obtained at rest cannot be extrapolated to what may occur during the behavior.⁸²

Electrical stimulation of a nucleus with short duration pulses (less than 1 ms) preferentially activates axons rather than somas.^{29,83} This results in the generation of axonal spikes and the consequent antidromic and orthodromic activation of subsets of distant neurons that send axons to the stimulated structure or are synaptically connected to it (see Fig. 1).

HFS-driven antidromic spikes collide with spontaneous orthodromic ones leading to the blockade of ongoing (pathological) activity in subpopulations of basal ganglia neurons, as long as the orthodromically propagated, spontaneous activity has a lower frequency than the HFS-driven one. This dual effect has been clearly shown in the STN,²² motor cortex,³⁷ GPe-GPi (Ammari et al. personal communication), and SNr³⁸ during STN-HFS, in ventral neurons of the thalamus during GPi-HFS³⁹ and suggested in the orbitofrontal cortex during accumbens-HFS.²⁴ An additional complication stems from the fact that activated axons also propagate spikes in the orthodromic direction and give rise to sustained neurotransmitter release.⁸⁴⁻⁸⁶ How postsynaptic responses (glutamatergic or GABAergic) follow a high frequency and long duration stimulation such as HFS is a question that still remains open, as the electrophysiological studies performed so far have only focused on relatively short-term stimula-tions. 23,39,62,75 The overall consequence of HFS on stimulated networks appears to be the generation of a new regular activity, locked to the stimulation but in a complex way. We propose that this HFS-driven activity decreases spontaneous pathological patterns, exacerbates the responsiveness to L-dopa and reverses several markers to control,^{58,87,88} yet preserves the transmission of cortical information.^{63,81}

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REFERENCES

- Hassler R, Riechert T, Mundinger F, Umbach W, Ganglberger JA. Physiological observations in stereotaxic operations in extrapyramidal motor disturbances. Brain 1960;83:337–350.
- Benabid AL, Pollak P, Gervason C, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 1991;337:403–406.
- Limousin P, Pollak P, Benazzouz A, et al. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 1995;345:91–95.

- Benabid AL, Deuschl G, Lang AE, Lyons KE, Rezai AR. Deep brain stimulation for Parkinson's disease. Mov Disord 2006;21 (Suppl 14):S168–S170.
- Rezai AR, Kopell BH, Gross RE, et al. Deep brain stimulation for Parkinson's disease: surgical issues. Mov Disord 2006;21 (Suppl 14):S197–S218.
- Kumar R, Dagher A, Hutchison WD, Lang AE, Lozano AM. Globus pallidus deep brain stimulation for generalized dystonia: clinical and PET investigation. Neurology 1999;53:871–874.
- Coubes P, Cif L, El FH, et al. Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. J Neurosurg 2004;101:189–194.
- Aouizerate B, Cuny E, Martin-Guehl C, et al. Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. J Neurosurg 2004;101:682–686.
- Lipsman N, Neimat JS, Lozano AM. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. Neurosurgery 2007;61:1–11.
- Houeto JL, Karachi C, Mallet L, et al. Tourette's syndrome and deep brain stimulation. J Neurol Neurosurg Psychiatry 2005;76: 992–995.
- Visser-Vandewalle V. DBS in Tourette syndrome: rationale, current status and future prospects. Acta Neurochir Suppl 2007;97 (Part 2):215–222.
- Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat Neurosci 2007;10:1116–1124.
- Priori A, Foffani G, Pesenti A, et al. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. Exp Neurol 2004;189:369–379.
- Raz A, Vaadia E, Bergman H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. J Neurosci 2000;20:8559– 8571.
- Sharott A, Magill PJ, Harnack D, Kupsch A, Meissner W, Brown P. Dopamine depletion increases the power and coherence of βoscillations in the cerebral cortex and subthalamic nucleus of the awake rat. Eur J Neurosci 2005;21:1413–1422.
- Gatev P, Darbin O, Wichmann T. Oscillations in the basal ganglia under normal conditions and in movement disorders. Mov Disord 2006;21:1566–1577.
- Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 2006;52:155–168.
- Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci 2007;30:357–364.
- McIntyre CC, Grill WM. Excitation of central nervous system neurons by nonuniform electric fields. Biophys J 1999;76:878– 888.
- Montgomery EB, Jr, Baker KB. Mechanisms of deep brain stimulation and future technical developments. Neurol Res 2000;22: 259–266.
- 21. Windels F, Bruet N, Poupard A, et al. Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. Eur J Neurosci 2000;12:4141–4146.
- Garcia L, Audin J, D'Alessandro G, Bioulac B, Hammond C. Dual effect of high-frequency stimulation on subthalamic neuron activity. J Neurosci 2003;23:8743–8751.
- Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosci 2003;23:1916–1923.
- 24. McCracken CB, Grace AA. High-frequency deep brain stimulation of the nucleus accumbens region suppresses neuronal activity and selectively modulates afferent drive in rat orbitofrontal cortex in vivo. J Neurosci 2007;27:12601–12610.

- Bolam JP, Hanley JJ, Booth PA, Bevan MD. Synaptic organisation of the basal ganglia. J Anat 2000;196 (Part 4):527–542.
- Luscher C, Nicoll RA, Malenka RC, Muller D. Synaptic plasticity and dynamic modulation of the postsynaptic membrane. Nat Neurosci 2000;3:545–550.
- Rizzone M, Lanotte M, Bergamasco B, et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: effects of variation in stimulation parameters. J Neurol Neurosurg Psychiatry 2001;71:215–219.
- Kuncel AM, Grill WM. Selection of stimulus parameters for deep brain stimulation. Clin Neurophysiol 2004;115:2431–2441.
- Ranck JB. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res 1975; 98:417–440.
- Holsheimer J, Dijkstra EA, Demeulemeester H, Nuttin B. Chronaxie calculated from current-duration and voltage-duration data. J Neurosci Methods 2000;97:45–50.
- Wallace BA, Ashkan K, Heise CE, et al. Survival of midbrain dopaminergic cells after lesion or deep brain stimulation of the subthalamic nucleus in MPTP-treated monkeys. Brain 2007;130 (Part 8):2129–2145.
- Haberler C, Alesch F, Mazal PR, et al. No tissue damage by chronic deep brain stimulation in Parkinson's disease. Ann Neurol 2000;48:372–376.
- 33. Tai CH, Boraud T, Bezard E, Bioulac B, Gross C, Benazzouz A. Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridles neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. FASEB J 2003;17:1820–1830.
- Meissner W, Leblois A, Hansel D, et al. Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. Brain 2005;128 (Part 10):2372–2382.
- Filali M, Hutchison WD, Palter VN, Lozano AM, Dostrovsky JO. Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. Exp Brain Res 2004;156:274–281.
- Welter ML, Houeto JL, Bonnet AM, et al. Effects of high-frequency stimulation on subthalamic neuronal activity in Parkinsonian patients. Arch Neurol 2004;61:89–96.
- Li S, Arbuthnott GW, Jutras MJ, Goldberg JA, Jaeger D. Resonant antidromic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. J Neurophysiol 2007;98:3525–3537.
- Maurice N, Thierry AM, Glowinski J, Deniau JM. Spontaneous and evoked activity of substantia nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. J Neurosci 2003;23:9929–9936.
- Montgomery EB, Jr. Effects of GPi stimulation on human thalamic neuronal activity. Clin Neurophysiol 2006;117:2691–2702.
- Garcia L, D'Alessandro G, Fernagut PO, Bioulac B, Hammond C. The impact of high frequency stimulation parameters on the pattern of discharge of subthalamic neurons. J Neurophysiol 2005; 94:3662–3669.
- Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J Neurophysiol 2001;85:1351–1356.
- McIntyre CC, Grill WM, Sherman DL, Thakor NV. Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. J Neurophysiol 2004;91:1457–1469.
- Chomiak T, Hu B. Axonal and somatic filtering of antidromically evoked cortical excitation by simulated deep brain stimulation in rat brain. J Physiol 2007;579 (Part 2):403–412.
- 44. Canteras NS, Shammah-Lagnado SJ, Silva BA, Ricardo JA. Afferent connections of the subthalamic nucleus: a combined retrograde and anterograde horseradish peroxidase study in the rat. Brain Res 1990;513:43–59.
- 45. Baker KB, Montgomery EB, Jr, Rezai AR, Burgess R, Luders HO. Subthalamic nucleus deep brain stimulus evoked potentials: physiological and therapeutic implications. Mov Disord 2002;17: 969–983.

- Cowan RL, Wilson CJ. Spontaneous firing patterns and axonal projections of single corticostriatal neurons in the rat medial agranular cortex. J Neurophysiol 1994;71:17–32.
- Grill WM, Cantrell MB, Robertson MS. Antidromic propagation of action potentials in branched axons: implications for the mechanisms of action of deep brain stimulation. J Comput Neurosci 2008;24:81–93.
- Sadek AR, Magill PJ, Bolam JP. A single-cell analysis of intrinsic connectivity in the rat globus pallidus. J Neurosci 2007;27: 6352–6362.
- Mailly P, Charpier S, Menetrey A, Deniau JM. Three-dimensional organization of the recurrent axon collateral network of the substantia nigra pars reticulata neurons in the rat. J Neurosci 2003;23:5247–5257.
- Hammond C, Rouzaire-Dubois B, Féger J, Jackson A, Crossman AR. Anatomical and electrophysiological studies on the reciprocal projections between the subthalamic nucleus and nucleus tegmenti pedunculopontinus in the rat. Neuroscience 1983;9:41– 52.
- 51. Florio T, Scarnati E, Confalone G, et al. High-frequency stimulation of the subthalamic nucleus modulates the activity of pedunculopontine neurons through direct activation of excitatory fibres as well as through indirect activation of inhibitory pallidal fibres in the rat. Eur J Neurosci 2007;25:1174–1186.
- 52. Kita H, Tachibana Y, Nambu A, Chiken S. Balance of monosynaptic excitatory and disynaptic inhibitory responses of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey. J Neurosci 2005;25:8611–8619.
- 53. Galati S, Mazzone P, Fedele E, et al. Biochemical and electrophysiological changes of substantia nigra pars reticulata driven by subthalamic stimulation in patients with Parkinson's disease. Eur J Neurosci 2006;23:2923–2928.
- Maltete D, Jodoin N, Karachi C, et al. Subthalamic stimulation and neuronal activity in the substantia nigra in Parkinson's disease. J Neurophysiol 2007;97:4017–4022.
- Temel Y, Visser-Vandewalle V, Kaplan S, et al. Protection of nigral cell death by bilateral subthalamic nucleus stimulation. Brain Res 2006;1120:100–105.
- Welter ML, Houeto JL, Tezenas du MS, et al. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain 2002;125 (Part 3):575–583.
- Moro E, Scerrati M, Romito LM, Roselli R, Tonali P, Albanese A. Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology 1999;53:85–90.
- Lacombe E, Carcenac C, Boulet S, et al. High-frequency stimulation of the subthalamic nucleus prolongs the increase in striatal dopamine induced by acute 1-3,4-dihydroxyphenylalanine in dopaminergic denervated rats. Eur J Neurosci 2007;26:1670– 1680.
- Meissner W, Harnack D, Reese R, et al. High-frequency stimulation of the subthalamic nucleus enhances striatal dopamine release and metabolism in rats. J Neurochem 2003;85:601– 609.
- Lee KH, Chang SY, Roberts DW, Kim U. Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. J Neurosurg 2004;101:511–517.
- Stefani A, Lozano AM, Peppe A, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 2007;130 (Part 6):1596–1607.
- 62. Bar-Gad I, Elias S, Vaadia E, Bergman H. Complex locking rather than complete cessation of neuronal activity in the globus pallidus of a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primate in response to pallidal microstimulation. J Neurosci 2004; 24:7410–7419.
- Degos B, Deniau JM, Thierry AM, Glowinski J, Pezard L, Maurice N. Neuroleptic-induced catalepsy: electrophysiological mechanisms of functional recovery induced by high-frequency stimulation of the subthalamic nucleus. J Neurosci 2005;25:7687– 7696.

- 64. Hariz MI, Krack P, Alesch F, et al. Multicentre European study of thalamic stimulation for Parkinsonian tremor, a 6-year followup. J Neurol Neurosurg Psychiatry (in press).
- Deuschl G, Bergman H. Pathophysiology of nonparkinsonian tremors. Mov Disord 2002;17 (Suppl 3):S41–S48.
- Anderson T, Hu B, Pittman Q, Kiss ZH. Mechanisms of deep brain stimulation: an intracellular study in rat thalamus. J Physiol 2004;559 (Part 1):301–313.
- Anderson TR, Hu B, Iremonger K, Kiss ZH. Selective attenuation of afferent synaptic transmission as a mechanism of thalamic deep brain stimulation-induced tremor arrest. J Neurosci 2006; 26:841–850.
- Bekar L, Libionka W, Tian GF, et al. Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. Nat Med 2008;14:75–80.
- Lozano AM, Kumar R, Gross RE, et al. Globus pallidus internus pallidotomy for generalized dystonia. Mov Disord 1997;12:865– 870.
- Wichmann T, Bergman H, Starr PA, Subramanian T, Watts RL, DeLong MR. Comparison of MPTP-induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia nigra pars reticulata in primates. Exp Brain Res 1999;125:397–409.
- Zhuang P, Li Y, Hallett M. Neuronal activity in the basal ganglia and thalamus in patients with dystonia. Clin Neurophysiol 2004; 115:2542–2557.
- Tang JK, Moro E, Mahant N, et al. Neuronal firing rates and patterns in the globus pallidus internus of patients with cervical dystonia differ from those with Parkinson's disease. J Neurophysiol 2007;98:720–729.
- Kupsch A, Benecke R, Muller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med 2006;355:1978–1990.
- 74. Vidailhet M, Vercueil L, Houeto JL, et al. Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. Lancet Neurol 2007;6:223– 229.
- Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol 2003;89: 1150–1160.
- Baxter LR, Jr, Phelps ME, Mazziotta JC, Guze BH, Schwartz JM, Selin CE. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. A comparison with rates in unipolar depression and in normal controls. Arch Gen Psychiatry 1987;44: 211–218.
- Swedo SE, Schapiro MB, Grady CL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Arch Gen Psychiatry 1989;46:518–523.
- Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. Br J Psychiatry Suppl 1998;35:26–37.
- Guehl D, Benazzouz A, Aouizerate B, et al. Neuronal correlates of obsessions in the caudate nucleus. Biol Psychiatry 2008;63: 557–562.
- Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet 1999;354: 1526.
- Mallet L, Schupbach M, N'Diaye K, et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. Proc Natl Acad Sci USA 2007;104:10661–10666.
- Montgomery EB, Jr, Gale JT. Mechanisms of action of deep brain stimulation (DBS). Neurosci Biobehav Rev 2008;32:388– 407.
- Nowak LG, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. I. Evidence from chronaxie measurements Exp Brain Res 1998;118:477–488.

- 84. Windels F, Bruet N, Poupard A, Feuerstein C, Bertrand A, Savasta M. Influence of the frequency parameter on extracellular glutamate and γ-aminobutyric acid in substantia nigra and globus pallidus during electrical stimulation of subthalamic nucleus in rats. J Neurosci Res 2003;72:259–267.
- Windels F, Carcenac C, Poupard A, Savasta M. Pallidal origin of GABA release within the substantia nigra pars reticulata during high-frequency stimulation of the subthalamic nucleus. J Neurosci 2005;25:5079–5086.
- 86. Lee KH, Kristic K, van HR, et al. High-frequency stimulation of the subthalamic nucleus increases glutamate in the subthalamic

nucleus of rats as demonstrated by in vivo enzyme-linked glutamate sensor. Brain Res 2007;1162:121-129.

- Meissner W, Guigoni C, Cirilli L, et al. Impact of chronic subthalamic high-frequency stimulation on metabolic basal ganglia activity: a 2-deoxyglucose uptake and cytochrome oxidase mRNA study in a macaque model of Parkinson's disease. Eur J Neurosci 2007;25:1492–1500.
- Oueslati A, Sgambato-Faure V, Melon C, et al. High-frequency stimulation of the subthalamic nucleus potentiates L-dopainduced neurochemical changes in the striatum in a rat model of Parkinson's disease. J Neurosci 2007;27:2377–2386.