Open access • Journal Article • DOI:10.1002/MDS.22120

Latest view on the mechanism of action of deep brain stimulation — Source link

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Published on: 15 Nov 2008 - Movement Disorders (John Wiley & Sons, Ltd)

Topics: Antidromic and Deep brain stimulation

Latest view on the mechanism of action of DBS

Journal:	*Movement Disorders*
Manuscript ID:	MDS-08-0001
Wiley - Manuscript type:	Review
Date Submitted by the Author:	02-Jan-2008
Complete List of Authors:	Hammond, Constance; INSERM, INMED Inserm Ammari, Rachida; Inserm, INMED Inserm Bioulac, Bernard; CNRS, UMR5227 Garcia, Liliana; CNRS, UMR5227
Keywords:	DBS, electrophysiology, Parkinson, dystonia, OCD

Latest view on the mechanism of action of deep brain stimulation

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Running title: Mechanisms of DBS

Key words: DBS, electrophysiology, antidromic spikes, Parkinson, Dystonia, OCD

Word count: title (65 letters & spaces), abstract (138 words),

Abstract

How does DBS alleviate symptoms of neurological disorders? Do the effects of DBS stem solely or even largely from local effects on the stimulated brain structure or are they also mediated by distal actions of DBS? Indeed, DBS as an extracellular stimulation is expected to preferentially activate axons leading to antidromic activation of local and afferent neurons. Antidromic spikes collide with ongoing spontaneous ones that propagate in the reverse (orthodromic) direction. Consequently, DBS decreases spontaneous pathological patterns. From their point of activation, DBS-evoked axonal spikes also propagate in the orthodromic direction but how synapses transmit DBS-driven patterns over the long term remains to be determined. Therefore, the best site of implantation of the DBS electrode may be in a region where the DBS-driven activity spreads to most of the identified, dysrhythmic, neuronal populations without causing additional side effects.

Introduction

Deep brain stimulation (DBS) has the potential to provide substantial benefit for various neurologic and neuropsychiatric diseases. DBS is an intracerebral, extracellular stimulation consisting of short pulses (in the order of 100 µs) regularly applied at a frequency of at least 100 Hz over a period of several years. First tested in ventral thalamic nuclei to alleviate essential tremor[1], it is now widely used in the internal pallidal segment (GPi) or subthalamic nucleus (STN) for Parkinson's disease[2-4], in the GPi for generalized dystonia[5,6], and more recently for other diseases such as treatment-resistant obsessive compulsive disorder (OCD)[7,8], Tourette syndrome[9,10] and depression[11]. 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 explanations have been proposed for the mechanism of action of DBS: (1) it silences stimulated neurons (i.e., it is equivalent to a local lesion) or (2) It introduces a new activity in the network. The first theory is based on the assumption that a group of neurons is responsible for the pathological activity of the whole network. Therefore silencing these neurons will immediately suppress the pathological activity. The second explanation leads to a different hypothesis: The whole network malfunctions for complex reasons but the injection in one point of a DBS-driven activity that propagates and consequently attenuates the pathological activity in many nuclei, may be beneficial as long as it does not activate too many undesirable regions. The clarification of the mechanisms of action of DBS is imperative to avoid implanting electrodes in regions having a low impact on clinical signs and/or leading to incapacitating side effects. In this review, we focus on results obtained within the last four years from multiunit and single cell electrophysiological recordings.

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

Increased synchronization and the appearance of oscillations in the activity patterns of populations of STN and GP neurons but also in motor cortical networks are salient aspects of Parkinsonism (PD). Pathological synchronization has been observed in human PD patients[12], 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys[13] and rodents with 6-hydroxydopamine (6-OHDA) lesions[14], suggesting functional alterations in the basal ganglia network. In particular increased coherence in the beta-band (13-30 Hz) is correlated with severity of symptoms in humans[15-17].

Mechanisms of STN-DBS have long been reduced to a lesion-like or inhibition hypothesis until in 2003, Hashimoto et al[18] and ourselves[19] from data obtained in two totally different preparations (MPTP-treated monkeys and slices from reserpine-treated rats, respectively) introduced the concept that high frequency stimulation drives neuronal activity in a pattern locked to the stimulation frequency or its sub harmonics and consequently erases pathological activity. This DBS-driven pattern could show alternated periods of activity and pauses and was observed only when stimulation parameters were clinically efficient[18] or close to the clinical ones[20]. On the light of studies performed during the late four years we will see whether this hypothesis is still valid and how it can be generalized.

The striatal network, the extrastriatal network and the place of the STN

Two networks can be distinguished within the basal ganglia, the striatal and the extrastriatal networks (Fig. 1). The striatal network lies in a single nucleus in rodents (the striatum), or in two nuclei in primates (caudate and putamen). It consists of GABAergic and cholinergic interneurons and GABAergic projection neurons. In contrast, the extrastriatal network is made up by five different neuronal populations, scattered in five different nuclei, the globus pallidus (external and internal), the subthalamic nucleus (STN) and the substantia nigra pars reticulata (SNr) and compacta (SNc). The link between the striatal and extrastriatal

networks is made by the projection neurons of the striatum, the GABAergic medium spiny neurons and in the reverse direction by the dopaminergic neurons of the SNc. The large reduction of the latter, due to the degeneration of nigro-striatal neurons, and the consequent loss of dopamine in the striatum, leads to 'typical' PD.

STN occupies a strategic position inside the extrastriatal network as STN neurons are the only glutamatergic neurons, they receive afferents from motor-related cortical areas, they project to all nuclei of the extrastriatal network including SNc dopaminergic neurons and are reciprocally connected with brainstem neurons of the pedunculopontine nucleus (PPN)[21].

Preparations and parameters of stimulation used to study STN-DBS are diverse

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

The question of the mechanisms of action of DBS relies on the analysis of what does a *high* frequency and *long* duration stimulation of neuronal elements (DBS is applied for years). Electrophysiologists are used to study synaptic potentials or currents 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 DBS 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[22], ultrashort (ms, s) and long (days, years) duration stimulations should evoke very different responses. Therefore, to evaluate the electrophysiological effects of STN-DBS, a compromise would be to stimulate and record for at least 30-60 minutes. To compare results from different studies, intensity of

stimulation is not as informative as current density (mA/cm^2). This parameter depends on the diameter of the stimulation electrode or contact and is not always available from papers. For this reason we never mention here the value of current intensity or density.

Is STN-DBS noxious to STN neurons?

Before analyzing the electrophysiological effect of STN-DBS, the first point to verify is the extent of STN lesion due to the chronic presence of the DBS electrode and 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 compared to the side that did not have the implant[23]. Therefore, the chronically-implanted DBS electrode does not induce local degenerescence and the beneficial effects of STN-DBS are not mediated by a lesion of the STN.

Does STN-DBS lock the electrophysiological activity of STN neurons to harmonics of the stimulation frequency?

Studies of the effect of STN-DBS 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 group recorded inhibition of STN neurons during STN-DBS in 6-OH DA rats[24] 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)[25]. In patients, STN-DBS of short durations decreased STN neurons activity[26] and changed the firing pattern of some STN neurons via a non-identified mechanism[27].

In slices STN activity is very low compared to 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 spikes and stimuli. In our experiments, all 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 gamma range frequency that totally erased spontaneous STN activity[19,20]. Interestingly, the fixed latency of DBS-driven spikes (close to 0 ms), the presence of the initial segment-somatodendritic (IS-SD) break in the recordings (Fig. 2A right) and the lack of effect of blockers of synaptic transmission, all strongly suggested that HFS-evoked spikes were antidromic (antidromic spikes propagate toward cell bodies i.e. in the direction opposite to physiological spikes that propagate in the orthodromic direction toward axon terminals). STN-DBS thus preferentially activated STN efferent axons probably at the level of their initial segment or first Ranvier node. Evoked antidromically propagated to STN somas where they were recorded (Fig. 1A, inset STN). Antidromic spikes by colliding with orthodromic, spontaneous ones erased STN spontaneous activity.

One possible explanation for the controversial results obtained in vivo and in vitro is that action potentials evoked in axons by local DBS, inefficiently invade cell bodies in the antidromic direction due to geometric ratio. DBS would therefore lead to active axons and silent somas[28,29]. 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[30]). 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-DBS antidromically activate afferent neurons to the STN?

A DBS electrode in a nucleus not only activates the efferent axons of local neurons but also the afferent axons. STN-DBS thus evokes antidromic spikes in neurons of the motor cortex and GP (Fig. 1). Axons passing through or near the STN can also be activated. Due to the 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 STN[31] displayed antidromic spikes (latency around 2 ms) whose frequency decreased with time to a steady state at around 40 Hz in response to 120 Hz STN stimulation[32] (Fig. 2B). Recordings of short latency evoked potentials over the motor cortex during STN-DBS also indicated that axons were most likely activated[33]. As glutamatergic cortico-subthalamic neurons give off many axon collaterals in deep and superficial layers[34] 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). But antidromic excitation of cortical networks may not be very efficient. For example, whereas the fast conducting branches in the highly myelinated brainstem region follow high frequency stimulation, the slower conducting fibres 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[29].

STN-HFS in slices (130 Hz, 90 µs) evoked antidromic spikes in GPe neurons with a mean latency of around 2 ms (Fig. 2C) that erased the ongoing activity in the recorded neurons. This may have consequences on neighbouring GPe neurons if the antidromic spikes propagate in the complex network of local GABAergic collaterals that synapse onto other GP neurons[35] (Fig. 1 inset GP).

STN-DBS also activates axons passing through and near the STN. Thus short STN-DBS (130 Hz, 60 µs, 30 s trains) in control rats *in vivo* antidromically activated a subpopulation of SNr neurons with a latency of around 1 ms[36], 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 recordings[36] probably via the activation of the complex network of intranigral collaterals between GABAergic SNr cells[37]. The same experiment has not been performed for SNc neurons.

In conclusion, STN-DBS antidromically activates subsets of neurons in the different nuclei that send axons to or close to the stimulated site. In that context, STN-DBS probably also antidromically activates PPN neurons that project to STN, though short trains of stimulation have only been tested at present[38,39]. Once evoked, antidromic axonal spikes propagate to their corresponding cell bodies at the stimulation frequency or its sub harmonics, 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 is difficult to guess as it needs to know the probability of propagation of antidromic spikes in axonal branches and how these spikes evoke synaptic responses at a long term.

Does STN-DBS orthodromically induce a complex locking of GP and SNr neuronal activity?

From their point of initiation, axonal spikes also propagate in the orthodromic direction toward axon terminals, i.e. along STN efferent axons (Fig. 1). Do these spikes evoke postsynaptic responses? STN-DBS 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)[18] (Fig. 3A). It thus shifted the firing pattern of GPe and GPi neurons, from irregular to

stimulus-synchronized and regular. The most probable mechanism 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[40].

Do GPi-DBS and STN-DBS have similar effects on GPi neurons since both ameliorate clinical signs of PD[41]? Bar-Gad et al[42] recorded the activity of GPe or GPi neurons in MPTP-treated monkeys in response to microstimulations applied in GPe or GPi (135 Hz, 200 µs, 600-3000 trains of 10 stimuli separated by 500 ms). They report in both GP a double excitation with latencies of 3 and 6 ms, separated by a short period of inhibition. Overall 70% of the neurons displayed locked activity i.e. they lost their basic firing pattern and switched to a predicted, orderly discharge that was locked to the stimulus. Again, a complex locking of target neurons activity is recorded.

Does STN-DBS similarly affect GP and SNr neurons? Deniau's group studied the spontaneous and evoked SNr activity before and during STN-DBS in control rats or rats treated with neuroleptics to block dopaminergic transmission. In control rats, STN-DBS (130 Hz, 60 µs, 30 s) evoked antidromic spikes and inhibition as previously seen but also orthodromic spikes (excitation) in SNr[36]. 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-DBS regularized the pattern of discharge of STN neurons as it significantly decreased the number of neurons exhibiting burst discharges and reduced the number of bursts emitted by bursting neurons. It also reversed to control the classical triphasic response to motor cortex stimulation[43]. Intracellular recordings from neurons in the pars compacta of the SN (SNc)

during short duration STN-DBS in slices revealed increased generation of EPSPs and increased frequency of action potentials[44].

In PD patients under surgical procedure, at parameters (130 Hz, 60 µs) that induce clinical improvement of rigidity and finger tapping, STN-DBS 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[45]. In another study STN-DBS (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[46].

Therefore, STN-DBS eliminates in some GP and SNr neurons the 'pathological' information encoded by the basal ganglia during PD and replaces it by a stimulus-driven firing pattern that is likely to contribute to the clinical motor improvements. This new activity would result, at least in part, from the activation of STN efferent fibres. The multiphasic pattern of the responses (alternated periods of excitation and inhibition) led some authors to suggest a participation of polysynaptic activity. This has to be confirmed since high frequency stimulations usually suppress polysynaptic responses. The exact mechanism of the complex responses recorded during short term STN-DBS or GP-DBS is not yet elucidated.

Does STN-DBS act on the survival and dopamine metabolism of remaining SNc neurons?

The rationale for testing the effect of STN-DBS on SNc neurons survival is the non tested hypothesis that glutamatergic inputs to SNc neurons, namely those from the STN[47,48] and PPN[38,49] would be excitotoxic to SNc dopaminergic neurons that have not yet degenerated, since both inputs are overactive in PD. The question then arised on whether STN-DBS protects remaining dopaminergic neurons from degeneration. This has been

investigated in murine and primate models of PD. Temel et al[50] 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-DBS (pulse width at 60 µs, frequency at 130 Hz, 1 h per day over a period of three months). This amount of STN modulation was sufficient to obtain a significant rescue of SNc dopaminergic neurons from cell death. Bilateral STN-DBS 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 non identical retrograde degeneration of SNc dopaminergic neurons in the different lesioned rats and thus did not result from STN-DBS. 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-DBS 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 DBS side serving as a control. They found around 20% more dopaminergic neurons in the SNc of the side that underwent DBS, compared to the non-DBS side. When the DBS electrode was located outside the STN, the difference between both sides was not significant[23]. Therefore STN-DBS 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-DBS in L-dopa responsive forms of Parkinson's disease and STN-DBS allows the discontinuation of L-Dopa or equivalent treatment or large reductions in daily dose[51] in contrast to GPi-DBS. The question therefore aroused whether STN-DBS favours dopamine release in the striatum. Savasta's group tested this hypothesis by measuring the extracellular content of dopamine and its metabolites in the striatum of rats that underwent a partial 6-OHDA lesion of one SNc[52]. After a delay of three weeks to allow the degeneration of 70 % of dopaminergic nigrostriatal

fibres 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 3 times the content of extracellular dopamine in the lesioned striatum measured with HPLC one hour after the injection. STN-DBS at clinical parameters (130 Hz, 60 µs, during one hour) amplified by around 100% this L-dopa-induced increase of dopamine during the stimulation period and for the following 2.5 h 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-DBS interacts in a synergistic manner with L-dopa. The underlying mechanisms have not been elucidated. The functional tone of the nigrostriatal DA system can be regulated at two sites, via inhibitory autoreceptors located on presynaptic dopaminergic terminals and controlling the synthesis or release of DA, and via receptors on the soma or dendrites of these neurones, involved in regulating impulse flow[53]. It seems plausible that STN-DBS has effects on the inputs coming from the STN to the somatodendritic receptors of SNc neurons. A simple explanation would be that STN-DBS acts by directly modulating the firing rate of dopaminergic neurones[54]. This, together with a decrease of inhibitory feedback regulation with the progression of nigrostriatal degeneration could stabilize the DA levels in the striatum in synergy with L-dopa.

STN-DBS regularizes neuronal activity in the extrastriatal network as well as in the motor cortex and amplifies L-dopa treatment

To conclude, STN-DBS due to the central position of the STN in the basal ganglia has multiple effects. It introduces a stimulation-locked, intermittent activity in many sites of the basal ganglia network (STN, motor cortex, GPe, GPi, SNr), mainly via antidromically propagated DBS-driven spikes and thus decreases ongoing pathological activity at these sites. This may also be valid for PPN and the good results obtained on axial motor signs with STN-

DBS in association with PPN-DBS[55], may result from a better regularization of PPN discharge pattern. Direct activation of passing fibres 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 DBS electrode active contact is in the dorsal part of the STN. Via a still unknown mechanism, STN-DBS protects dopaminergic neurons that have not yet degenerated and ameliorates the endogenous release of dopamine in the striatum when applied concomitantly with L-dopa treatment. This last hypothesis on dopamine release is strengthened by the fact that only patients responding to L-dopa are good candidates for STN-DBS. Conversely, this may imply that STN is not a good target for DBS in the case of dopamine-independent disorders.

DBS for other neurological disorders

DBS in motor cortico-basal ganglia-thalamocortical loop for essential tremor

DBS of ventral nuclei of the thalamus can dramatically relieve essential tremor in the majority of patients[1,56]. Essential tremor is thought to arise from dysfunction of the glutamatergic olivocerebellar pathway which projects to ventral thalamic (VL) nuclei[57]. VL-HFS in rat brain slices silenced thalamic relay neurons after a transient period of intense depolarization[58]. 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 (EPSPs) at 5 Hz in the recorded VL neuron. A concomitant short duration HFS (125 Hz, for 10 s) in one locus only totally suppressed the 5 Hz EPSPs in the HFS-stimulated pathway but not in the non-stimulated one, suggesting that HFS selectively disrupts afferent synaptic transmission[59].

DBS in motor cortico-basal ganglia-thalamocortical loop for dystonia

Neuronal activity is altered in basal ganglia and ventral thalamic nuclei in dystonia[60]. The firing pattern of GPi neurons known to be regular in monkeys[61] consists in patients of irregular grouped discharges with intermittent pauses and a third of the neurons discharge at the frequency of the electromyogram[62,63]. Neurons in ventral oralis posterior / intermediate nuclei of the thalamus (Vop/Vim) have a sustained activity at 130-150 Hz, organized in bursts lasting from 500 ms to 5 s and recurring at a frequency similar to that of dystonia frequency[62].

DBS for medically intractable forms of dystonia has been tested in GPi[64], STN[65] and VL nuclei of the thalamus[66]. GPi-DBS is now currently used for primary generalized DYT-1 positive dystonia and idiopathic cervical dystonia[6,67,68]. In contrast to Parkinson's disease, the beneficial effects of DBS 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 t0, or in control animals, owing to the lack of reliable animal models of dystonia.

During short duration GPi-DBS, 50 to 70% Vop neurons of the thalamus reduced their average discharge frequency with a delay of a few ms in control monkeys[69] or dystonic patients[30], suggesting that DBS activates GPi efferent axons that are GABAergic and inhibitory onto thalamic neurons (Fig. 3B). Moreover, 88% of Vop neurons were antidromically activated with a 1 ms latency probably as a result of the activation of axons originating in Vop and passing in the vicinity of the GPi-DBS electrode (Fig. 2E).

DBS 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[70-72]. Recently, a dramatic increase in neuronal activity of the ventral caudate nucleus was identified and correlated to the patients' self-evaluated obsessions[73]. DBS of the ventral anterior internal capsule[74,75] or accumbens[7] are therapeutic approaches for treatment-resistant

OCD. DBS mechanisms were studied with imaging techniques in patients and electrophysiological techniques in control rats as robust animal models of OCD are lacking.

DBS of the accumbens (130 Hz, 200 µs, 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[76]. The authors suggest that antidromic spikes propagate in axonal collaterals of cortical neurons and thus evoke inhibitory responses in neighbouring neurons via GABAergic interneurons (Fig. 1, inset cortex). But this has still to be demonstrated as antidromic axonal spikes often inefficiently invade axon collaterals and somas[29].

CONCLUSION

Electrical stimulation of a nucleus with short duration pulses (less than 1 ms) preferentially activates axons rather than somas[77,78]. This results in the generation of axonal spikes and antidromic activation of local cell bodies via their efferent axons as well as distant cell bodies that send axons to the stimulated structure (Fig. 1). DBS-driven antidromic spikes collide with spontaneous orthodromic ones leading to the blockade of ongoing (pathological) activity. This dual effect has been clearly shown in the STN[19], motor cortex[32], GPe-GPi (Ammari et al personal communication) and SNr[36] during STN-DBS, in ventral neurons of the thalamus during GPi-DBS[30] and suggested in the orbitofrontal cortex during accumbens-DBS[76]. An additional complication stems from the fact that activated axons also propagate spikes in the orthodromic direction and give rise to sustained neurotransmitter release[79-81]. How postsynaptic responses (glutamatergic or GABAergic) follow a *high* frequency and *long* duration stimulation such as DBS is a question that still remains open, as the electrophysiological studies performed so far have only focused on relatively short term stimulations[18,30,42,69]. The overall consequence of DBS on stimulated networks appears to be

the generation of a new activity, locked to the stimulation but with a lower frequency and interspersed pauses. This DBS-driven activity significantly attenuates the spontaneous pathological one, exacerbates the responsiveness to L-dopa and reverses several markers to control[52,82,83], yet preserves the transmission of cortical information[43,76].

Acknowledgements

This work was supported by Institut National de la Recherche Médicale (Inserm), Fondation de France and Association France Parkinson.

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Legends

Figure 1: STN and the striatal and extrastriatal networks

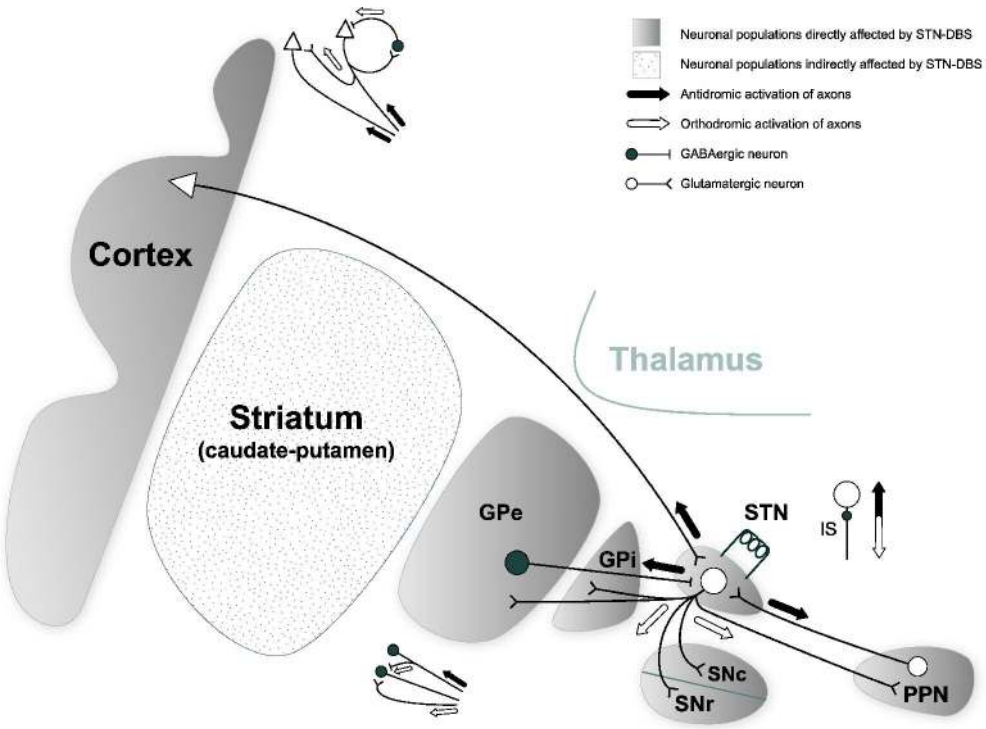
STN-DBS preferentially activates axons thus generating spikes that propagate in the antidromic (towards STN, motor cortex, GPe & PPN somas) and orthodromic (towards GPe, GPi, SNr, SNc, PPN) directions. Passing fibers can also be activated. As a result, all the nuclei of the extrastriatal network and motor cortical areas are directly affected by STN-DBS. The striatal network is indirectly affected via the modulation of dopaminergic neurons of the SNc. 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 cortical[76] and GPe networks).

Figure 2 DBS-driven antidromic spikes

Antidromic responses in (A) 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) (B) Motor cortical neurons in response to STN-DBS (arrow head indicates collision, right)[32], (C) GPe neurons in response to STN-HFS (Ammari et al, unpublished data) (D) SNr neurons in response to STN-DBS (note collision, bottom trace, right)[36], (E) Vop thalamic neurons in response to GPi-DBS (post-stimulus raster plot, top; histogram, bottom; antidromic spikes, right)[30].

Figure 3: DBS-driven orthodromic responses

Orthodromic responses of (A) GPi neurons in response to STN-DBS (complex sequence of excitation-inhibition-excitation)[18], (B) Vop thalamic neurons in response to GPi-DBS (antidromic activation followed by a complex sequence of excitation-inhibition-excitation, post stimulus rater, top and histogram, bottom)[30].



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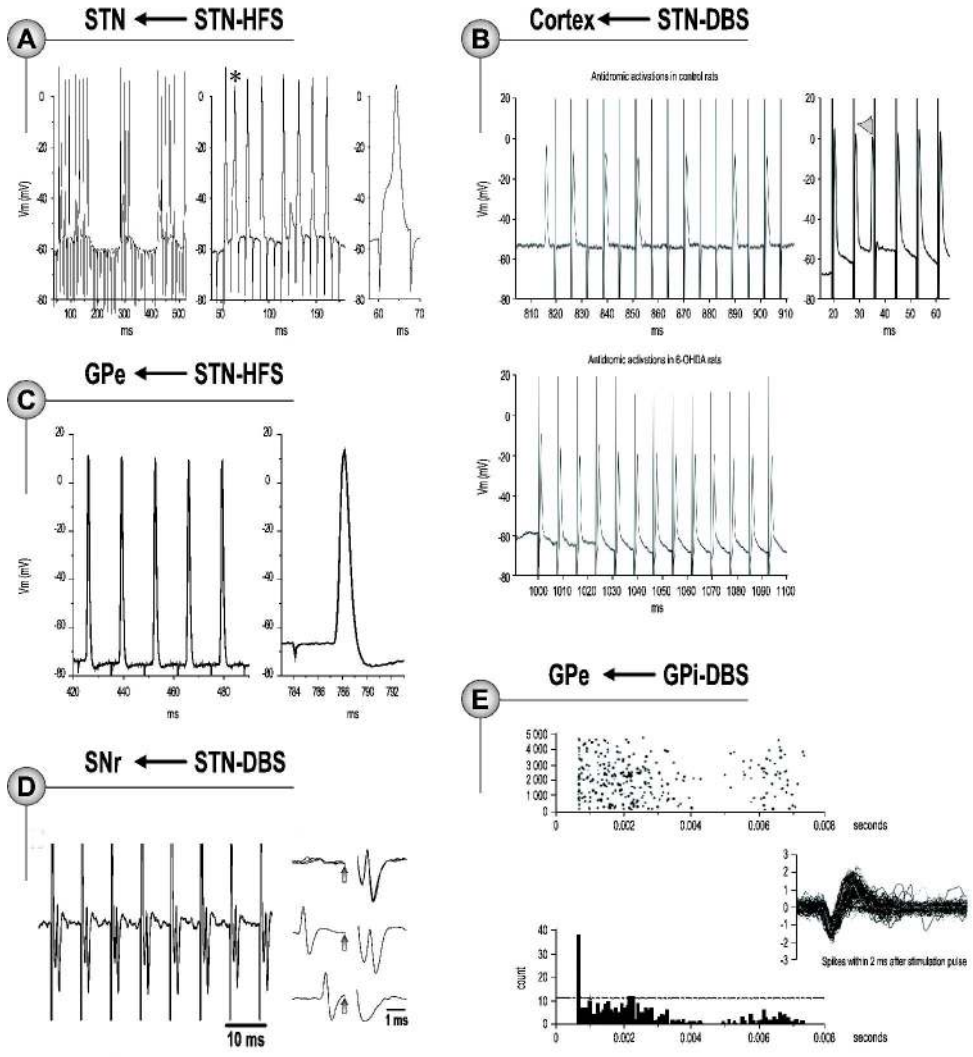

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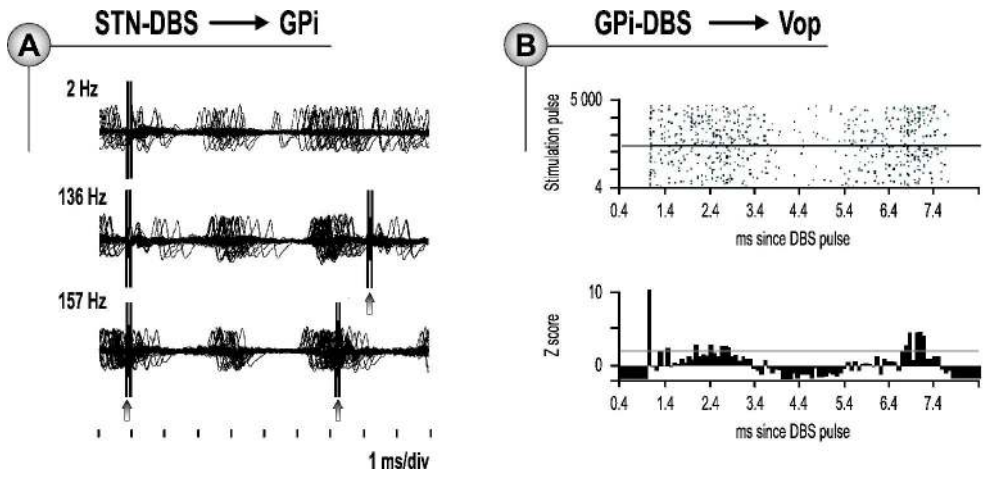

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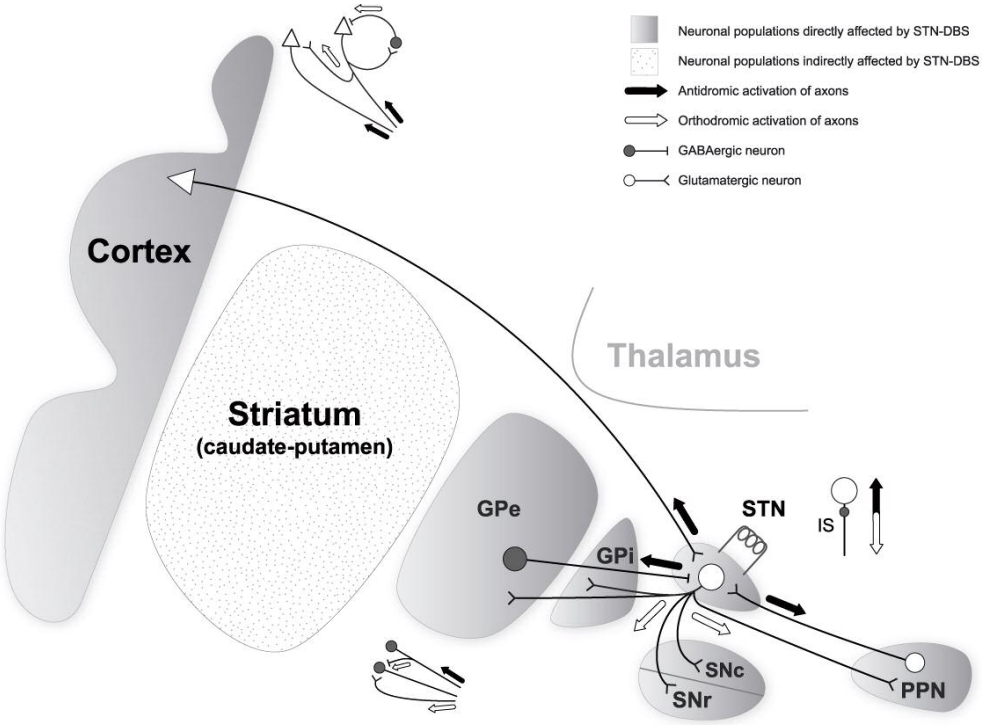

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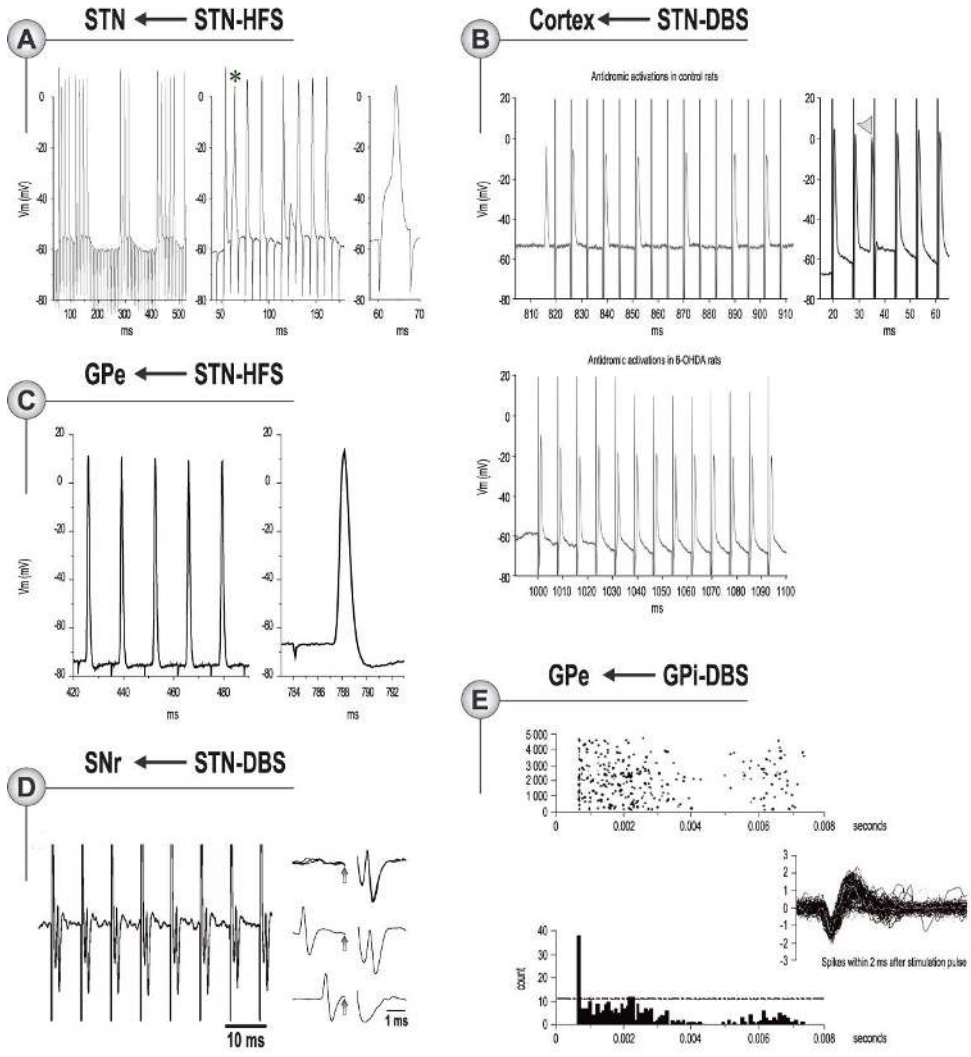

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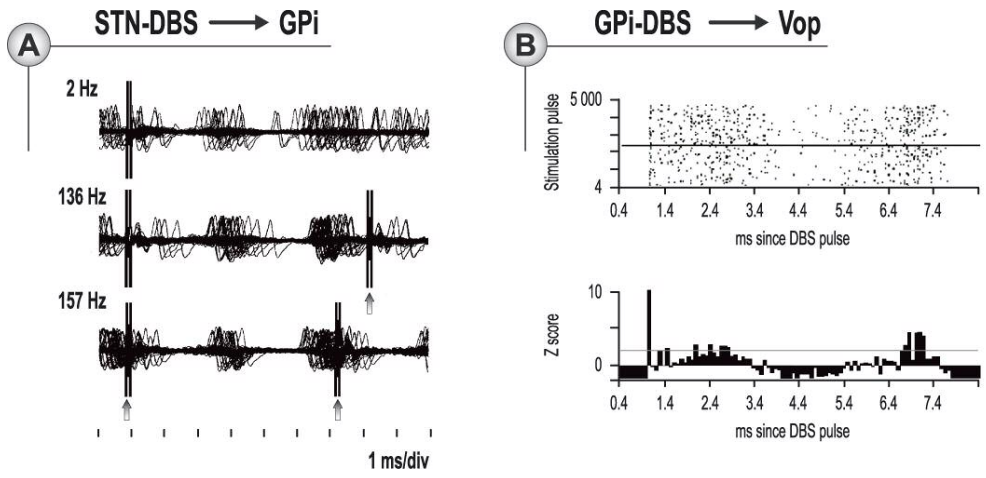

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