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Latest view on the mechanism of action of DBS

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review

Latest view on the mechanism of action of deep brain stimulation

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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 μ s) 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 tremor¹, it is now widely used in the internal pallidal segment (GPi) or subthalamic nucleus (STN) for Parkinson's disease²⁻⁴, 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 depression¹¹. 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 patients¹², 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys¹³ and rodents with 6-hydroxydopamine (6-OHDA) lesions¹⁴, 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 humans¹⁵⁻¹⁷.

Mechanisms of STN-DBS have long been reduced to a lesion-like or inhibition hypothesis until in 2003, Hashimoto et al¹⁸ and ourselves¹⁹ 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 efficient¹⁸ or close to the clinical ones²⁰. 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

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3 networks is made by the projection neurons of the striatum, the GABAergic medium spiny
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5 neurons and in the reverse direction by the dopaminergic neurons of the SNc. The large
6
7 reduction of the latter, due to the degeneration of nigro-striatal neurons, and the consequent
8
9 loss of dopamine in the striatum, leads to 'typical' PD.
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13 STN occupies a strategic position inside the extrastriatal network as STN neurons are
14
15 the only glutamatergic neurons, they receive afferents from motor-related cortical areas, they
16
17 project to all nuclei of the extrastriatal network including SNc dopaminergic neurons and are
18
19 reciprocally connected with brainstem neurons of the pedunculopontine nucleus (PPN)²¹.
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22 23 24 **Preparations and parameters of stimulation used to study STN-DBS are diverse**

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26 Different types of preparations have been used to study DBS mechanisms, from
27
28 anesthetized *in vivo* models of PD to *in vitro* slices. Each preparation has its own advantages
29
30 and pitfalls but their combination should allow understanding DBS mechanisms as long as we
31
32 keep aware of the limitations of the technique used. In the present review DBS refers to high
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34 frequency stimulations *in vivo* and HFS to that *in vitro*.
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39 The question of the mechanisms of action of DBS relies on the analysis of what does a
40
41 *high* frequency and *long* duration stimulation of neuronal elements (DBS is applied for years).
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43 Electrophysiologists are used to study synaptic potentials or currents in response to single
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45 stimulations but here the question is far more complex mainly for technical reasons as
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47 recordings have to be maintained for minutes or hours and spikes identified among artifacts. If
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49 all studies on DBS mechanisms test high frequency (100-180 Hz) stimuli, they rarely apply
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51 them for *long* durations. Considering synaptic plasticity (potentiation or depression) that
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53 usually occurs in synaptic transmission after tetanic stimulation²², ultrashort (ms, s) and long
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55 (days, years) duration stimulations should evoke very different responses. Therefore, to
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57 evaluate the electrophysiological effects of STN-DBS, a compromise would be to stimulate
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59 and record for at least 30-60 minutes. To compare results from different studies, intensity of
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3 stimulation is not as informative as current density (mA/cm^2). This parameter depends on the
4 diameter of the stimulation electrode or contact and is not always available from papers. For
5 this reason we never mention here the value of current intensity or density.
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10 11 12 **Is STN-DBS noxious to STN neurons?**

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14 Before analyzing the electrophysiological effect of STN-DBS, the first point to verify
15 is the extent of STN lesion due to the chronic presence of the DBS electrode and stimulation.
16
17 The classical Medtronic electrode was implanted in one STN in control or MPTP-treated
18 monkeys, and the stimulation continuously applied for 7 months (pulses at 130 Hz, 60 μs
19 duration). Cell counts performed in Nissl-stained coronal sections of the STN showed that the
20 STN having the implant had only 5% difference in total cell number compared to the side that
21 did not have the implant²³. Therefore, the chronically-implanted DBS electrode does not
22 induce local degeneration and the beneficial effects of STN-DBS are not mediated by a
23 lesion of the STN.
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38 **Does STN-DBS lock the electrophysiological activity of STN neurons to harmonics** 39 **of the stimulation frequency?**

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42 Studies of the effect of STN-DBS locally on STN neurons gave the most controversial
43 data. This probably results from the difficulty to separate the very short latency evoked spikes
44 from the stimulation artifacts or as we will see later on the difference between cell body and
45 axonal activity in some conditions. Benazzouz group recorded inhibition of STN neurons
46 during STN-DBS in 6-OH DA rats²⁴ but recently described that this inhibition only lasted 4
47 ms after each stimulus when the interval between two stimuli was fixed at 7.7 ms (130 Hz)²⁵.
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49 In patients, STN-DBS of short durations decreased STN neurons activity²⁶ and changed the
50 firing pattern of some STN neurons via a non-identified mechanism²⁷.
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3 In slices STN activity is very low compared to that *in vivo* and does not show the
4 pathological alterations resulting from dopamine depletion probably because the basal ganglia
5 network is absent in coronal slices. Slices have however the advantage of allowing
6 intracellular recordings and precise analysis of the correspondence between spikes and
7 stimuli. In our experiments, all STN spontaneous spikes disappeared during STN-HFS and
8 were replaced by spikes evoked by and locked to stimuli (Fig. 2A). The STN firing pattern
9 under HFS consisted of trains of evoked spikes in the gamma range frequency that totally
10 erased spontaneous STN activity^{19,20}. Interestingly, the fixed latency of DBS-driven spikes
11 (close to 0 ms), the presence of the initial segment-somatodendritic (IS-SD) break in the
12 recordings (Fig. 2A right) and the lack of effect of blockers of synaptic transmission, all
13 strongly suggested that HFS-evoked spikes were antidromic (antidromic spikes propagate
14 toward cell bodies i.e. in the direction opposite to physiological spikes that propagate in the
15 orthodromic direction toward axon terminals). STN-DBS thus preferentially activated STN
16 efferent axons probably at the level of their initial segment or first Ranvier node. Evoked
17 antidromically propagated to STN somas where they were recorded (Fig. 1A, inset STN).
18 Antidromic spikes by colliding with orthodromic, spontaneous ones erased STN spontaneous
19 activity.
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43 One possible explanation for the controversial results obtained *in vivo* and *in vitro* is
44 that action potentials evoked in axons by local DBS, inefficiently invade cell bodies in the
45 antidromic direction due to geometric ratio. DBS would therefore lead to active axons and
46 silent somas^{28,29}. Since extracellular microelectrode recordings are biased toward recording
47 action potentials from cell bodies rather than axons, this would result in the appearance of
48 decreased activity within the stimulated structure though efferent axons are excited (see
49 discussion in³⁰). In contrast intracellular or juxtacellular recordings record axonal spikes
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3 evoked at the level of the initial segment (IS spikes, Fig. 2A middle) and higher intensities of
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5 stimulation would compensate for the geometric ratio.
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10 **Does STN-DBS antidromically activate afferent neurons to the STN?**
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12 A DBS electrode in a nucleus not only activates the efferent axons of local neurons but
13
14 also the afferent axons. STN-DBS thus evokes antidromic spikes in neurons of the motor
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16 cortex and GP (Fig. 1). Axons passing through or near the STN can also be activated. Due to
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18 the low probability of antidromic invasion of somas, antidromic spikes are usually evoked in a
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20 subset of afferent neurons only.
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24 So, a subset of layer V/VI neurons of motor cortex, that project to STN³¹ displayed
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26 antidromic spikes (latency around 2 ms) whose frequency decreased with time to a steady
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28 state at around 40 Hz in response to 120 Hz STN stimulation³² (Fig. 2B). Recordings of short
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30 latency evoked potentials over the motor cortex during STN-DBS also indicated that axons
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32 were most likely activated³³. As glutamatergic cortico-subthalamic neurons give off many
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34 axon collaterals in deep and superficial layers³⁴ that contact other projection neurons and local
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36 GABAergic interneurons, antidromic invasion of a subset of neurons may retrogradely affect
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38 cortical circuits in complex ways (Fig. 1 inset cortex). But antidromic excitation of cortical
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40 networks may not be very efficient. For example, whereas the fast conducting branches in the
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42 highly myelinated brainstem region follow high frequency stimulation, the slower conducting
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44 fibres in the poorly myelinated thalamic region fail to transmit consecutive antidromic spikes
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46 and maintain a steady low-frequency (6-12 Hz) spike output during the stimulation²⁹.
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52 STN-HFS in slices (130 Hz, 90 μ s) evoked antidromic spikes in GPe neurons with a
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54 mean latency of around 2 ms (Fig. 2C) that erased the ongoing activity in the recorded
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56 neurons. This may have consequences on neighbouring GPe neurons if the antidromic spikes
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58 propagate in the complex network of local GABAergic collaterals that synapse onto other GP
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60 neurons³⁵ (Fig. 1 inset GP).

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3 STN-DBS also activates axons passing through and near the STN. Thus short STN-
4 DBS (130 Hz, 60 μ s, 30 s trains) in control rats *in vivo* antidromically activated a
5 subpopulation of SNr neurons with a latency of around 1 ms³⁶, probably as a result of the
6 activation of ascending SNr axons. This decreased the spontaneous activity of the
7 antidromically activated SNr neurons and inhibited other SNr neurons as shown in
8 recordings³⁶ probably via the activation of the complex network of intranigral collaterals
9 between GABAergic SNr cells³⁷. The same experiment has not been performed for SNc
10 neurons.
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22 In conclusion, STN-DBS antidromically activates subsets of neurons in the different
23 nuclei that send axons to or close to the stimulated site. In that context, STN-DBS probably
24 also antidromically activates PPN neurons that project to STN, though short trains of
25 stimulation have only been tested at present^{38,39}. Once evoked, antidromic axonal spikes
26 propagate to their corresponding cell bodies at the stimulation frequency or its sub harmonics,
27 may also propagate in recurrent axonal collaterals and activate synaptic transmission that
28 impinges onto other projection neurons (GP, SNr) or local interneurons (see Fig.1, insets
29 cortex and GPe). The overall result on a network is difficult to guess as it needs to know the
30 probability of propagation of antidromic spikes in axonal branches and how these spikes
31 evoke synaptic responses at a long term.
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Does STN-DBS orthodromically induce a complex locking of GP and SNr neuronal activity?

50 From their point of initiation, axonal spikes also propagate in the orthodromic
51 direction toward axon terminals, i.e. along STN efferent axons (Fig. 1). Do these spikes evoke
52 postsynaptic responses? STN-DBS parameters that improved spontaneous movements and
53 muscle tone (130, 210 μ s, 25 s-5 min) in MPTP-treated monkeys, evoked stimulus-locked
54 double excitatory responses at latencies around 4 and 6 ms in the globus pallidus (GPe and
55 GPi)¹⁸ (Fig. 3A). It thus shifted the firing pattern of GPe and GPi neurons, from irregular to
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3 stimulus-synchronized and regular. The most probable mechanism is the orthodromic
4 activation of STN efferent axons projecting to GP, the release of glutamate and the
5 monosynaptic excitation of postsynaptic GPe or GPi neurons. In contrast, in control monkeys,
6 bursts of 100 Hz stimuli (10 pulses) induced powerful excitatory responses in the GPe but
7 inhibition in the GPi attributed to the activation of the disynaptic STN-GPe-GPi pathway⁴⁰.
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15 Do GPi-DBS and STN-DBS have similar effects on GPi neurons since both ameliorate
16 clinical signs of PD⁴¹? Bar-Gad et al⁴² recorded the activity of GPe or GPi neurons in MPTP-
17 treated monkeys in response to microstimulations applied in GPe or GPi (135 Hz, 200 μ s,
18 600-3000 trains of 10 stimuli separated by 500 ms). They report in both GP a double
19 excitation with latencies of 3 and 6 ms, separated by a short period of inhibition. Overall 70%
20 of the neurons displayed locked activity i.e. they lost their basic firing pattern and switched to
21 a predicted, orderly discharge that was locked to the stimulus. Again, a complex locking of
22 target neurons activity is recorded.
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34 Does STN-DBS similarly affect GP and SNr neurons? Deniau's group studied the
35 spontaneous and evoked SNr activity before and during STN-DBS in control rats or rats
36 treated with neuroleptics to block dopaminergic transmission. In control rats, STN-DBS (130
37 Hz, 60 μ s, 30 s) evoked antidromic spikes and inhibition as previously seen but also
38 orthodromic spikes (excitation) in SNr³⁶. The short latency excitation is likely to result from
39 the orthodromic activation of the excitatory STN-SNr glutamatergic axon terminals. In
40 cataleptic rats, at parameters that reversed the catalepsy (130 Hz, 60-80 μ s), STN-DBS
41 regularized the pattern of discharge of STN neurons as it significantly decreased the number
42 of neurons exhibiting burst discharges and reduced the number of bursts emitted by bursting
43 neurons. It also reversed to control the classical triphasic response to motor cortex
44 stimulation⁴³. Intracellular recordings from neurons in the pars compacta of the SN (SNc)
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3 during short duration STN-DBS in slices revealed increased generation of EPSPs and
4 increased frequency of action potentials⁴⁴.
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8 In PD patients under surgical procedure, at parameters (130 Hz, 60 μ s) that induce
9 clinical improvement of rigidity and finger tapping, STN-DBS increased mean spike
10 frequency of SNr neurons and evoked short latency (4 ms) excitatory responses.
11 Autocorrelograms demonstrated the presence of a periodic spiking at 130 Hz. In parallel the
12 firing pattern changed from irregular to a 'grouped' pattern consisting of groups of spikes
13 separated by longer periods of pauses⁴⁵. In another study STN-DBS (140 Hz, 60 μ s) evoked
14 in SNr neurons a three phase sequence, inhibition (0-2 ms) - excitation (2-4 ms) - inhibition
15 (4-7 ms) after the stimulation pulse. There was a 51% decrease in the percentage of the spikes
16 contributing to bursts and a 70% decrease in the mean duration of bursting mode activity⁴⁶.
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29 Therefore, STN-DBS eliminates in some GP and SNr neurons the 'pathological'
30 information encoded by the basal ganglia during PD and replaces it by a stimulus-driven
31 firing pattern that is likely to contribute to the clinical motor improvements. This new activity
32 would result, at least in part, from the activation of STN efferent fibres. The multiphasic
33 pattern of the responses (alternated periods of excitation and inhibition) led some authors to
34 suggest a participation of polysynaptic activity. This has to be confirmed since high frequency
35 stimulations usually suppress polysynaptic responses. The exact mechanism of the complex
36 responses recorded during short term STN-DBS or GP-DBS is not yet elucidated.
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50 **Does STN-DBS act on the survival and dopamine metabolism of remaining SNc neurons?**

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52 The rationale for testing the effect of STN-DBS on SNc neurons survival is the non
53 tested hypothesis that glutamatergic inputs to SNc neurons, namely those from the STN^{47,48}
54 and PPN^{38,49} would be excitotoxic to SNc dopaminergic neurons that have not yet
55 degenerated, since both inputs are overactive in PD. The question then arised on whether
56 STN-DBS protects remaining dopaminergic neurons from degeneration. This has been
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3 investigated in murine and primate models of PD. Temel et al⁵⁰ injected 6-OHDA at four sites
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5 in both striatum of rats. During the phase of ongoing neurodegeneration in the SNc, half of
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7 the lesioned rats were treated with bilateral STN-DBS (pulse width at 60 μ s, frequency at 130
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9 Hz, 1 h per day over a period of three months). This amount of STN modulation was
10
11 sufficient to obtain a significant rescue of SNc dopaminergic neurons from cell death.
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13 Bilateral STN-DBS not only had a protective effect on the number of TH positive neurons but
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15 also on the total number of neurons in the SNc. It could be argued that this effect resulted
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17 from a non identical retrograde degeneration of SNc dopaminergic neurons in the different
18
19 lesioned rats and thus did not result from STN-DBS. For this reason, to mimic the clinical
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21 situation and to be able to observe neuroprotection, Benabid's group performed a subacute
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23 model of MPTP treatment in primates and induced a symmetrical 50% reduction of Nissl-
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25 stained and TH positive cells in the two SNc. They applied a unilateral STN-DBS after MPTP
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27 treatment and compared the number of Nissl-stained and TH-positive SNc cells between each
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29 side of the brain in two animals, the non DBS side serving as a control. They found around
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31 20% more dopaminergic neurons in the SNc of the side that underwent DBS, compared to the
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33 non-DBS side. When the DBS electrode was located outside the STN, the difference between
34
35 both sides was not significant²³. Therefore STN-DBS may have offered neuroprotection to
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37 nigral dopaminergic neurons that would have degenerated as part of the disease process.
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46 Several studies reported an excellent clinical outcome of STN-DBS in L-dopa
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48 responsive forms of Parkinson's disease and STN-DBS allows the discontinuation of L-Dopa
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50 or equivalent treatment or large reductions in daily dose⁵¹ in contrast to GPi-DBS. The
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52 question therefore aroused whether STN-DBS favours dopamine release in the striatum.
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54 Savasta's group tested this hypothesis by measuring the extracellular content of dopamine and
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56 its metabolites in the striatum of rats that underwent a partial 6-OHDA lesion of one SNc⁵².
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58 After a delay of three weeks to allow the degeneration of 70 % of dopaminergic nigrostriatal
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3 fibres in the dorsolateral part of the striatum, they implanted the stimulation electrode in the
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5 STN and the microdialysis probe in the striatum, both ipsilateral to the lesion. The i.p.
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7 injection of L-dopa (50 mg/kg) increased by around 3 times the content of extracellular
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9 dopamine in the lesioned striatum measured with HPLC one hour after the injection. STN-
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11 DBS at clinical parameters (130 Hz, 60 μ s, during one hour) amplified by around 100% this
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13 L-dopa-induced increase of dopamine during the stimulation period and for the following 2.5
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15 h after the end of stimulation. In contrast, in intact animals, L-dopa failed to enhance the
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17 extracellular dopamine levels during the stimulation period. This suggests that STN-DBS
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19 interacts in a synergistic manner with L-dopa. The underlying mechanisms have not been
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21 elucidated. The functional tone of the nigrostriatal DA system can be regulated at two sites,
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23 via inhibitory autoreceptors located on presynaptic dopaminergic terminals and controlling
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25 the synthesis or release of DA, and via receptors on the soma or dendrites of these neurones,
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27 involved in regulating impulse flow⁵³. It seems plausible that STN-DBS has effects on the
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29 inputs coming from the STN to the somatodendritic receptors of SNc neurons. A simple
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31 explanation would be that STN-DBS acts by directly modulating the firing rate of
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33 dopaminergic neurones⁵⁴. This, together with a decrease of inhibitory feedback regulation
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35 with the progression of nigrostriatal degeneration could stabilize the DA levels in the striatum
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37 in synergy with L-dopa.
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48 **STN-DBS regularizes neuronal activity in the extrastriatal network as well as in the motor cortex**
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50 **and amplifies L-dopa treatment**
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52 To conclude, STN-DBS due to the central position of the STN in the basal ganglia has
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54 multiple effects. It introduces a stimulation-locked, intermittent activity in many sites of the
55
56 basal ganglia network (STN, motor cortex, GPe, GPi, SNr), mainly via antidromically
57
58 propagated DBS-driven spikes and thus decreases ongoing pathological activity at these sites.
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60 This may also be valid for PPN and the good results obtained on axial motor signs with STN-

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3 DBS in association with PPN-DBS⁵⁵, may result from a better regularization of PPN
4 discharge pattern. Direct activation of passing fibres dorsal to the STN and in particular nigro-
5 striatal and pallido-thalamic axons may also participate to the beneficial effect as the best
6 position of the DBS electrode active contact is in the dorsal part of the STN. Via a still
7 unknown mechanism, STN-DBS protects dopaminergic neurons that have not yet degenerated
8 and ameliorates the endogenous release of dopamine in the striatum when applied
9 concomitantly with L-dopa treatment. This last hypothesis on dopamine release is
10 strengthened by the fact that only patients responding to L-dopa are good candidates for STN-
11 DBS. Conversely, this may imply that STN is not a good target for DBS in the case of
12 dopamine-independent disorders.
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31 **DBS for other neurological disorders**

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

33 DBS of ventral nuclei of the thalamus can dramatically relieve essential tremor in the majority
34 of patients^{1,56}. Essential tremor is thought to arise from dysfunction of the glutamatergic
35 olivocerebellar pathway which projects to ventral thalamic (VL) nuclei⁵⁷. VL-HFS in rat brain
36 slices silenced thalamic relay neurons after a transient period of intense depolarization⁵⁸. The
37 authors hypothesized that VL-HFS introduced a functional deafferentation of stimulated
38 neurons, thereby stopping tremor from propagating to thalamo-cortical loops. To test whether
39 this depression of afferent synaptic transmission is selective, they stimulated at 5 Hz in two
40 different loci within the VL to mimic afferent stimuli at tremor frequency. Both stimulations
41 evoked excitatory postsynaptic potentials (EPSPs) at 5 Hz in the recorded VL neuron. A
42 concomitant short duration HFS (125 Hz, for 10 s) in one locus only totally suppressed the 5
43 Hz EPSPs in the HFS-stimulated pathway but not in the non-stimulated one, suggesting that
44 HFS selectively disrupts afferent synaptic transmission⁵⁹.
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DBS in motor cortico-basal ganglia-thalamocortical loop for dystonia

Neuronal activity is altered in basal ganglia and ventral thalamic nuclei in dystonia⁶⁰. The firing pattern of GPi neurons known to be regular in monkeys⁶¹ 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 frequency⁶².

DBS for medically intractable forms of dystonia has been tested in GPi⁶⁴, STN⁶⁵ and VL nuclei of the thalamus⁶⁶. GPi-DBS is now currently used for primary generalized DYT-1 positive dystonia and idiopathic cervical dystonia^{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 monkeys⁶⁹ or dystonic patients³⁰, 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 rest⁷⁰⁻⁷². Recently, a dramatic increase in neuronal activity of the ventral caudate nucleus was identified and correlated to the patients' self-evaluated obsessions⁷³. DBS of the ventral anterior internal capsule^{74,75} or accumbens⁷ are therapeutic approaches for treatment-resistant

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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 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 axons⁷⁶. 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 somas²⁹.

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 STN¹⁹, motor cortex³², GPe-GPi (Ammari et al personal communication) and SNr³⁶ during STN-DBS, in ventral neurons of the thalamus during GPi-DBS³⁰ and suggested in the orbitofrontal cortex during accumbens-DBS⁷⁶. An additional complication stems from the fact that activated axons also propagate spikes in the orthodromic direction and give rise to sustained neurotransmitter release⁷⁹⁻⁸¹. 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

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

17 **Figure 1: STN and the striatal and extrastriatal networks**

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21 STN-DBS preferentially activates axons thus generating spikes that propagate in the
22 antidromic (towards STN, motor cortex, GPe & PPN somas) and orthodromic (towards GPe,
23 GPi, SNr, SNc, PPN) directions. Passing fibers can also be activated. As a result, all the
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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 cortical⁷⁶ and GPe networks).

42 **Figure 2 DBS-driven antidromic spikes**

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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.

For Peer Review

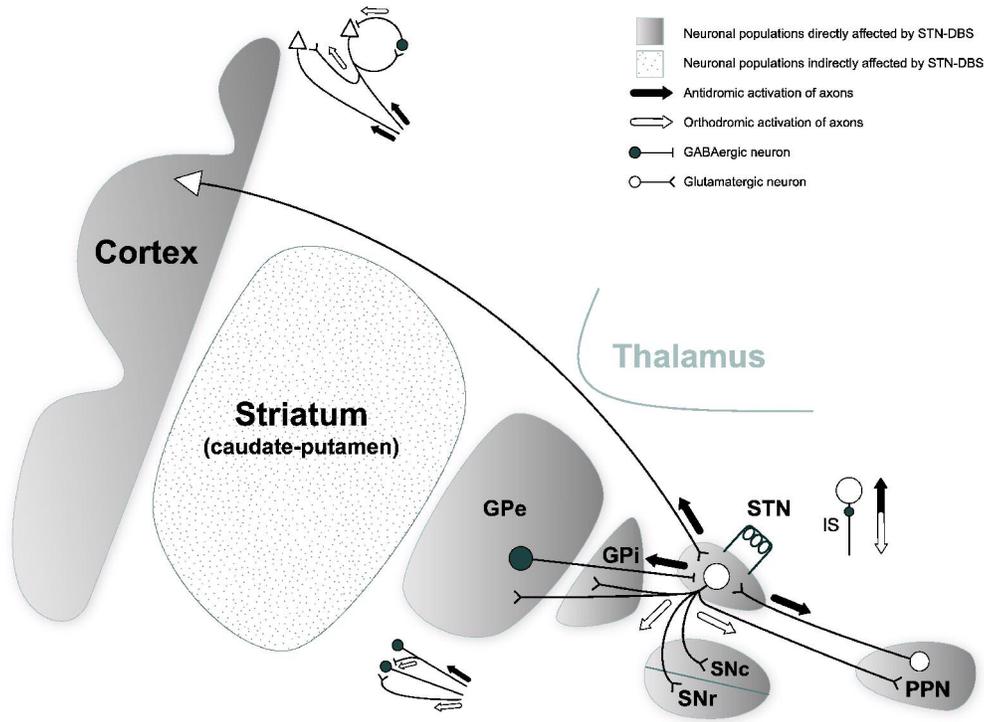


Figure 1: STN and the striatal and extrastriatal networks STN-DBS preferentially activates axons thus generating spikes that propagate in the antidromic (towards STN, motor cortex, GPe & PPN somas) and orthodromic (towards GPe, GPi, SNr, SNc, PPN) directions. Passing fibers can also be activated. As 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 cortical⁷⁶ and GPe networks).

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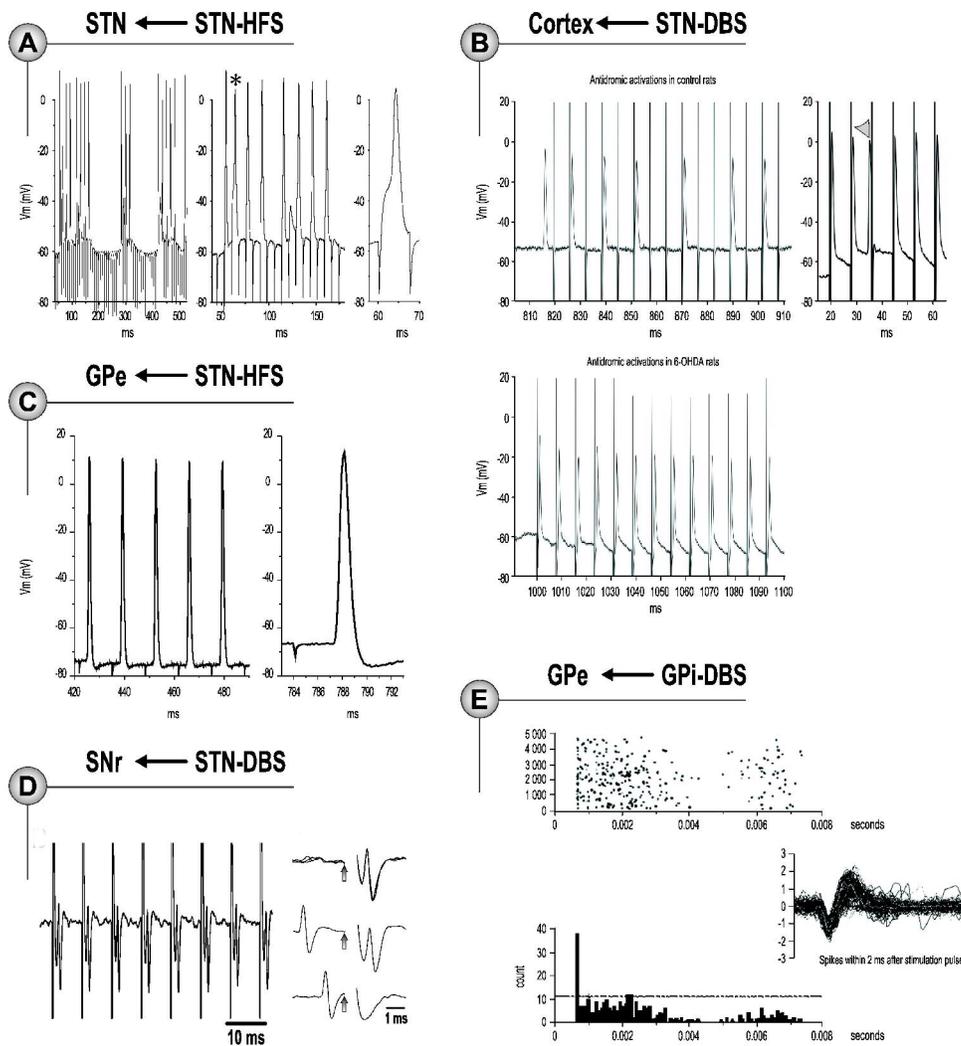


Figure 2 DBS-driven antidromic spikes Antidromic responses in (A) STN neurons in response to STN-HFS (note IS spike at $t=120$ ms, middle and IS-SD break, right) (Garcia et al, unpublished figure) (B) Motor cortical neurons in response to STN-DBS (arrow head indicates collision, right)³², (C) GPe neurons 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.

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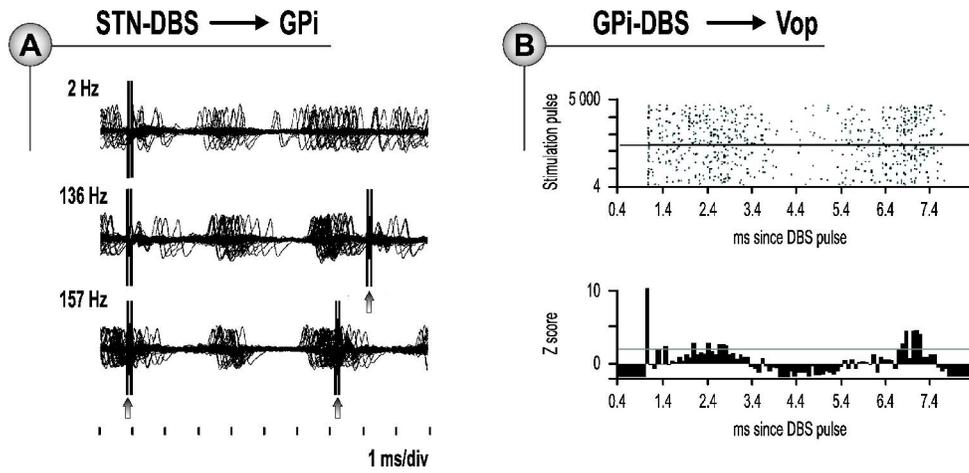


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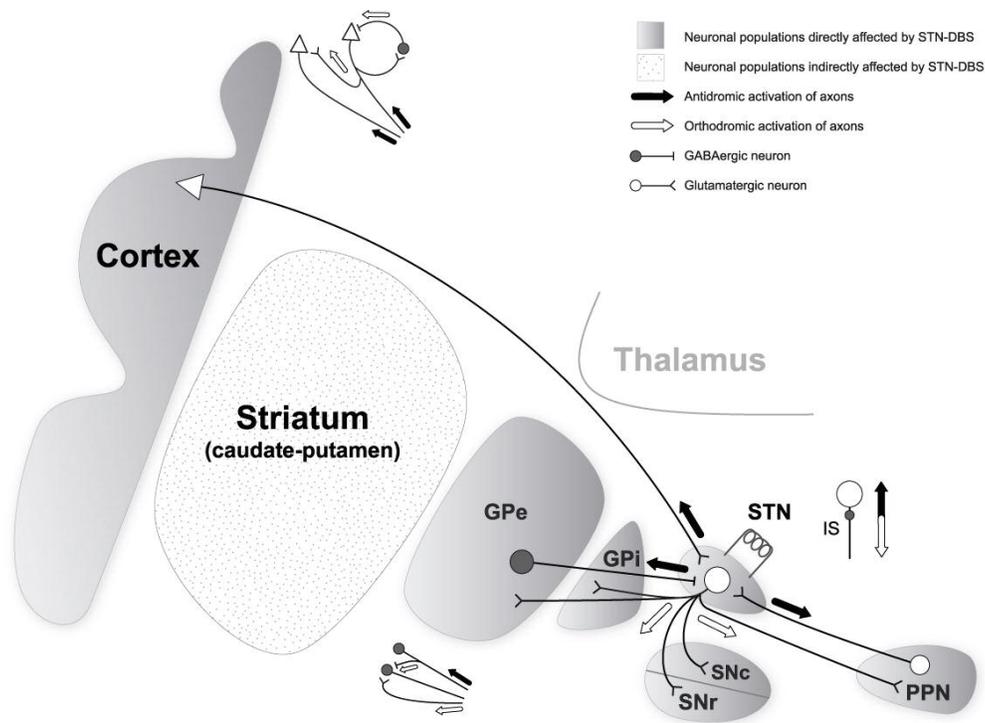


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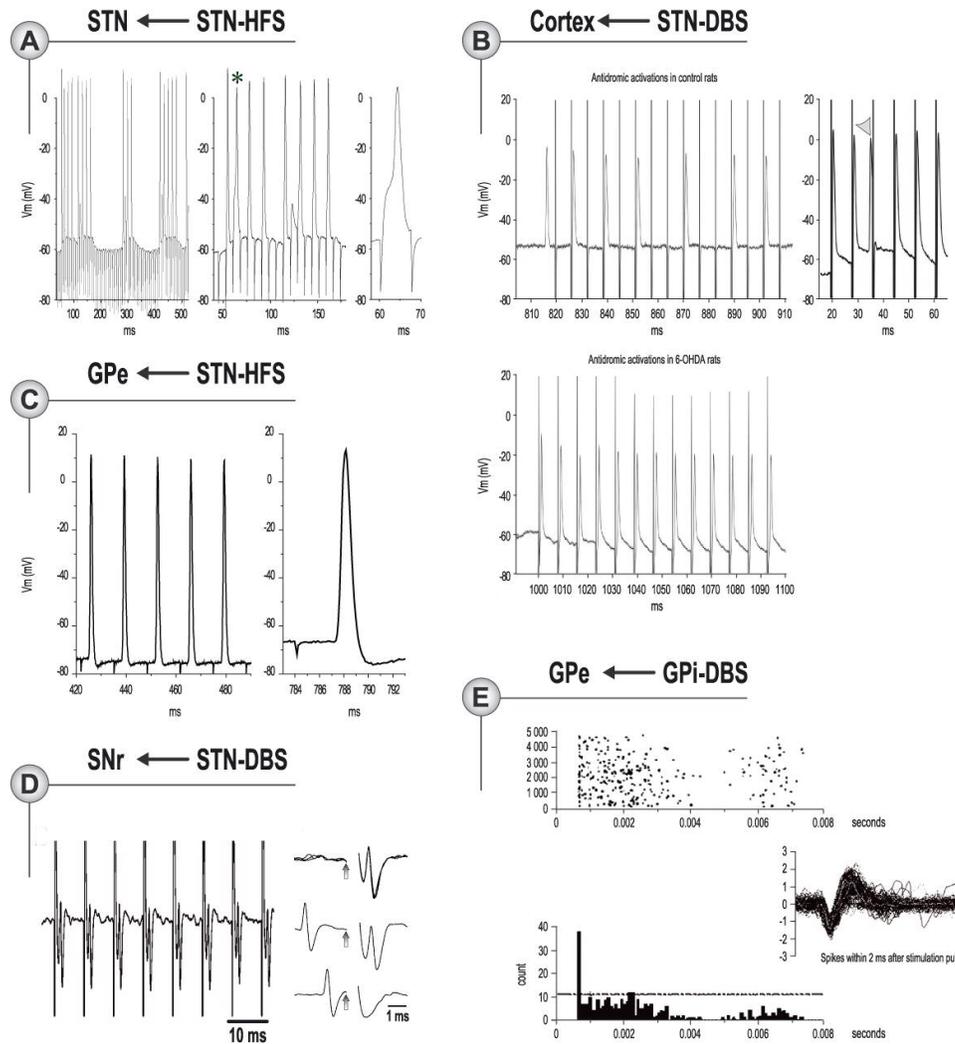


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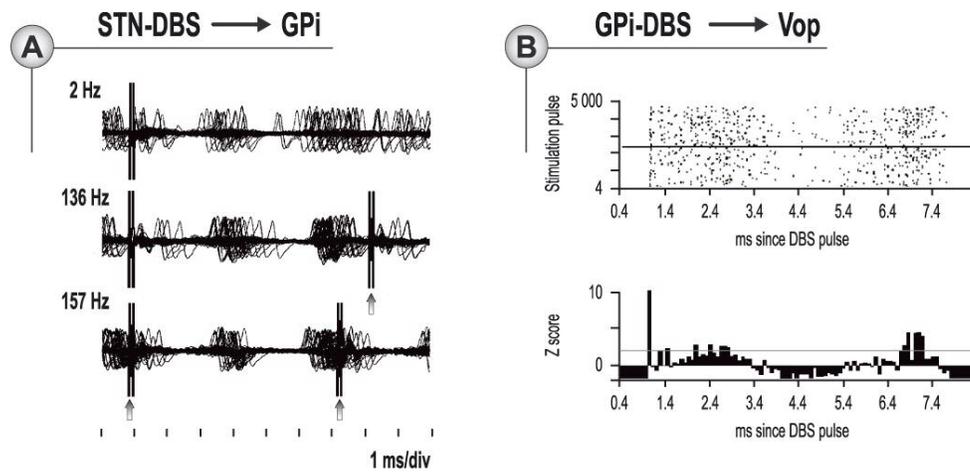


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