



HAL
open science

Latest view on the mechanism of action of deep brain stimulation.

Constance Hammond, Rachida Ammari, Bernard Bioulac, Liliana Garcia

► To cite this version:

Constance Hammond, Rachida Ammari, Bernard Bioulac, Liliana Garcia. Latest view on the mechanism of action of deep brain stimulation.. *Movement Disorders*, 2008, 23 (15), pp.2111-21. 10.1002/mds.22120 . inserm-02950812

HAL Id: inserm-02950812

<https://inserm.hal.science/inserm-02950812>

Submitted on 28 Sep 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Latest view on the mechanism of action of DBS

Journal:	<i>Movement Disorders</i>
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



review

Latest view on the mechanism of action of deep brain stimulation

Constance Hammond¹, Rachida Ammari^{1,2}, Bernard Bioulac² and Liliana Garcia²

¹ Institut de Neurobiologie de la Méditerranée (INMED), Unité mixte Inserm-Université Aix Marseille II, 163 route de Luminy, BP13, 13273 Marseille Cédex 9, France.

² UMR 5227 CNRS-Université Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux Cédex, France.

Corresponding author:

Constance Hammond, INMED Inserm, 163 route de Luminy, BP13, 13273 Marseille Cédex 9, France. Tel: 33 4 91 82 81 10, fax: 33 4 91 82 81 01

email: hammond@inmed.univ-mrs.fr

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 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

1
2
3 networks is made by the projection neurons of the striatum, the GABAergic medium spiny
4
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.
10
11

12
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.
20
21

22 23 24 **Preparations and parameters of stimulation used to study STN-DBS are diverse**

25
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
33
34 frequency stimulations *in vivo* and HFS to that *in vitro*.
35
36
37

38
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).
42
43 Electrophysiologists are used to study synaptic potentials or currents in response to single
44
45 stimulations but here the question is far more complex mainly for technical reasons as
46
47 recordings have to be maintained for minutes or hours and spikes identified among artifacts. If
48
49 all studies on DBS mechanisms test high frequency (100-180 Hz) stimuli, they rarely apply
50
51 them for *long* durations. Considering synaptic plasticity (potentiation or depression) that
52
53 usually occurs in synaptic transmission after tetanic stimulation²², ultrashort (ms, s) and long
54
55 (days, years) duration stimulations should evoke very different responses. Therefore, to
56
57 evaluate the electrophysiological effects of STN-DBS, a compromise would be to stimulate
58
59 and record for at least 30-60 minutes. To compare results from different studies, intensity of
60

1
2
3 stimulation is not as informative as current density (mA/cm²). 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.
6
7
8
9

10 11 12 **Is STN-DBS noxious to STN neurons?**

13
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 The classical Medtronic electrode was implanted in one STN in control or MPTP-treated
17 monkeys, and the stimulation continuously applied for 7 months (pulses at 130 Hz, 60 μ s
18 duration). Cell counts performed in Nissl-stained coronal sections of the STN showed that the
19 STN having the implant had only 5% difference in total cell number compared to the side that
20 did not have the implant²³. Therefore, the chronically-implanted DBS electrode does not
21 induce local degeneration and the beneficial effects of STN-DBS are not mediated by a
22 lesion of the STN.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37

38 **Does STN-DBS lock the electrophysiological activity of STN neurons to harmonics** 39 **of the stimulation frequency?**

40
41 Studies of the effect of STN-DBS locally on STN neurons gave the most controversial
42 data. This probably results from the difficulty to separate the very short latency evoked spikes
43 from the stimulation artifacts or as we will see later on the difference between cell body and
44 axonal activity in some conditions. Benazzouz group recorded inhibition of STN neurons
45 during STN-DBS in 6-OH DA rats²⁴ but recently described that this inhibition only lasted 4
46 ms after each stimulus when the interval between two stimuli was fixed at 7.7 ms (130 Hz)²⁵.
47 In patients, STN-DBS of short durations decreased STN neurons activity²⁶ and changed the
48 firing pattern of some STN neurons via a non-identified mechanism²⁷.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
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.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

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
50
51
52
53
54
55
56
57
58
59
60

1
2
3 evoked at the level of the initial segment (IS spikes, Fig. 2A middle) and higher intensities of
4
5 stimulation would compensate for the geometric ratio.
6
7
8

9
10 **Does STN-DBS antidromically activate afferent neurons to the STN?**
11

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
15
16 cortex and GP (Fig. 1). Axons passing through or near the STN can also be activated. Due to
17
18 the low probability of antidromic invasion of somas, antidromic spikes are usually evoked in a
19
20 subset of afferent neurons only.
21
22

23
24 So, a subset of layer V/VI neurons of motor cortex, that project to STN³¹ displayed
25
26 antidromic spikes (latency around 2 ms) whose frequency decreased with time to a steady
27
28 state at around 40 Hz in response to 120 Hz STN stimulation³² (Fig. 2B). Recordings of short
29
30 latency evoked potentials over the motor cortex during STN-DBS also indicated that axons
31
32 were most likely activated³³. As glutamatergic cortico-subthalamic neurons give off many
33
34 axon collaterals in deep and superficial layers³⁴ that contact other projection neurons and local
35
36 GABAergic interneurons, antidromic invasion of a subset of neurons may retrogradely affect
37
38 cortical circuits in complex ways (Fig. 1 inset cortex). But antidromic excitation of cortical
39
40 networks may not be very efficient. For example, whereas the fast conducting branches in the
41
42 highly myelinated brainstem region follow high frequency stimulation, the slower conducting
43
44 fibres in the poorly myelinated thalamic region fail to transmit consecutive antidromic spikes
45
46 and maintain a steady low-frequency (6-12 Hz) spike output during the stimulation²⁹.
47
48
49
50
51

52 STN-HFS in slices (130 Hz, 90 μ s) evoked antidromic spikes in GPe neurons with a
53
54 mean latency of around 2 ms (Fig. 2C) that erased the ongoing activity in the recorded
55
56 neurons. This may have consequences on neighbouring GPe neurons if the antidromic spikes
57
58 propagate in the complex network of local GABAergic collaterals that synapse onto other GP
59
60 neurons³⁵ (Fig. 1 inset GP).

1
2
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.
11
12
13
14
15
16
17
18
19
20
21

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.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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

51 From their point of initiation, axonal spikes also propagate in the orthodromic
52 direction toward axon terminals, i.e. along STN efferent axons (Fig. 1). Do these spikes evoke
53 postsynaptic responses? STN-DBS parameters that improved spontaneous movements and
54 muscle tone (130, 210 μ s, 25 s-5 min) in MPTP-treated monkeys, evoked stimulus-locked
55 double excitatory responses at latencies around 4 and 6 ms in the globus pallidus (GPe and
56 GPi)¹⁸ (Fig. 3A). It thus shifted the firing pattern of GPe and GPi neurons, from irregular to
57
58
59
60

1
2
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.
8
9

10
11
12
13
14
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.
23
24
25
26
27
28
29
30
31
32

33
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)
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 during short duration STN-DBS in slices revealed increased generation of EPSPs and
4 increased frequency of action potentials⁴⁴.
5
6

7
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.
17
18
19
20
21
22
23
24
25
26
27
28

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.
37
38
39
40
41
42
43
44
45
46
47
48
49

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

51
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
57
58
59
60

1
2
3 investigated in murine and primate models of PD. Temel et al⁵⁰ injected 6-OHDA at four sites
4
5 in both striatum of rats. During the phase of ongoing neurodegeneration in the SNc, half of
6
7 the lesioned rats were treated with bilateral STN-DBS (pulse width at 60 μ s, frequency at 130
8
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.
12
13 Bilateral STN-DBS not only had a protective effect on the number of TH positive neurons but
14
15 also on the total number of neurons in the SNc. It could be argued that this effect resulted
16
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
20
21 situation and to be able to observe neuroprotection, Benabid's group performed a subacute
22
23 model of MPTP treatment in primates and induced a symmetrical 50% reduction of Nissl-
24
25 stained and TH positive cells in the two SNc. They applied a unilateral STN-DBS after MPTP
26
27 treatment and compared the number of Nissl-stained and TH-positive SNc cells between each
28
29 side of the brain in two animals, the non DBS side serving as a control. They found around
30
31 20% more dopaminergic neurons in the SNc of the side that underwent DBS, compared to the
32
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
36
37 nigral dopaminergic neurons that would have degenerated as part of the disease process.
38
39
40
41
42
43
44

45
46 Several studies reported an excellent clinical outcome of STN-DBS in L-dopa
47
48 responsive forms of Parkinson's disease and STN-DBS allows the discontinuation of L-Dopa
49
50 or equivalent treatment or large reductions in daily dose⁵¹ in contrast to GPi-DBS. The
51
52 question therefore aroused whether STN-DBS favours dopamine release in the striatum.
53
54 Savasta's group tested this hypothesis by measuring the extracellular content of dopamine and
55
56 its metabolites in the striatum of rats that underwent a partial 6-OHDA lesion of one SNc⁵².
57
58 After a delay of three weeks to allow the degeneration of 70 % of dopaminergic nigrostriatal
59
60

1
2
3 fibres in the dorsolateral part of the striatum, they implanted the stimulation electrode in the
4
5 STN and the microdialysis probe in the striatum, both ipsilateral to the lesion. The i.p.
6
7 injection of L-dopa (50 mg/kg) increased by around 3 times the content of extracellular
8
9 dopamine in the lesioned striatum measured with HPLC one hour after the injection. STN-
10
11 DBS at clinical parameters (130 Hz, 60 μ s, during one hour) amplified by around 100% this
12
13 L-dopa-induced increase of dopamine during the stimulation period and for the following 2.5
14
15 h after the end of stimulation. In contrast, in intact animals, L-dopa failed to enhance the
16
17 extracellular dopamine levels during the stimulation period. This suggests that STN-DBS
18
19 interacts in a synergistic manner with L-dopa. The underlying mechanisms have not been
20
21 elucidated. The functional tone of the nigrostriatal DA system can be regulated at two sites,
22
23 via inhibitory autoreceptors located on presynaptic dopaminergic terminals and controlling
24
25 the synthesis or release of DA, and via receptors on the soma or dendrites of these neurones,
26
27 involved in regulating impulse flow⁵³. It seems plausible that STN-DBS has effects on the
28
29 inputs coming from the STN to the somatodendritic receptors of SNc neurons. A simple
30
31 explanation would be that STN-DBS acts by directly modulating the firing rate of
32
33 dopaminergic neurones⁵⁴. This, together with a decrease of inhibitory feedback regulation
34
35 with the progression of nigrostriatal degeneration could stabilize the DA levels in the striatum
36
37 in synergy with L-dopa.
38
39
40
41
42
43
44
45
46
47

48 **STN-DBS regularizes neuronal activity in the extrastriatal network as well as in the motor cortex**
49
50 **and amplifies L-dopa treatment**
51

52 To conclude, STN-DBS due to the central position of the STN in the basal ganglia has
53
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.
59
60 This may also be valid for PPN and the good results obtained on axial motor signs with STN-

1
2
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.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

30 **DBS for other neurological disorders**

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

32 DBS of ventral nuclei of the thalamus can dramatically relieve essential tremor in the majority
33 of patients^{1,56}. Essential tremor is thought to arise from dysfunction of the glutamatergic
34 olivocerebellar pathway which projects to ventral thalamic (VL) nuclei⁵⁷. VL-HFS in rat brain
35 slices silenced thalamic relay neurons after a transient period of intense depolarization⁵⁸. The
36 authors hypothesized that VL-HFS introduced a functional deafferentation of stimulated
37 neurons, thereby stopping tremor from propagating to thalamo-cortical loops. To test whether
38 this depression of afferent synaptic transmission is selective, they stimulated at 5 Hz in two
39 different loci within the VL to mimic afferent stimuli at tremor frequency. Both stimulations
40 evoked excitatory postsynaptic potentials (EPSPs) at 5 Hz in the recorded VL neuron. A
41 concomitant short duration HFS (125 Hz, for 10 s) in one locus only totally suppressed the 5
42 Hz EPSPs in the HFS-stimulated pathway but not in the non-stimulated one, suggesting that
43 HFS selectively disrupts afferent synaptic transmission⁵⁹.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
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}.
7
8
9
10
11

12 **Acknowledgements**

13
14 This work was supported by Institut National de la Recherche Médicale (Inserm), Fondation
15 de France and Association France Parkinson.
16
17
18
19
20

21 **REFERENCES**

- 22 1. Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M et al. Long-term suppression of
23 tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 1991, 337(8738):403-
24 406.
25
- 26 2. Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E et al. Effect of parkinsonian
27 signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 1995, 345(8942):91-5.
28
- 29 3. Benabid AL, Deuschl G, Lang AE, Lyons KE, Rezaï AR. Deep brain stimulation for Parkinson's disease.
30 *Mov Disord* 2006, 21 Suppl 14:S168-S170.
31
- 32 4. Rezaï AR, Kopell BH, Gross RE, Vitek JL, Sharan AD, Limousin P et al. Deep brain stimulation for
33 Parkinson's disease: surgical issues. *Mov Disord* 2006, 21 Suppl 14:S197-S218.
34
- 35 5. Kumar R, Dagher A, Hutchison WD, Lang AE, Lozano AM. Globus pallidus deep brain stimulation for
36 generalized dystonia: clinical and PET investigation. *Neurology* 1999, 53(4):871-874.
37
- 38 6. Coubes P, Cif L, El FH, Hemm S, Vayssiere N, Serrat S et al. Electrical stimulation of the globus pallidus
39 internus in patients with primary generalized dystonia: long-term results. *J Neurosurg* 2004, 101(2):189-
40 194.
41
- 42 7. Aouizerate B, Cuny E, Martin-Guehl C, Guehl D, Amieva H, Benazzouz A et al. Deep brain stimulation
43 of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression.
44 Case report. *J Neurosurg* 2004, 101(4):682-686.
45
- 46 8. Lipsman N, Neimat JS, Lozano AM. Deep brain stimulation for treatment-refractory obsessive-
47 compulsive disorder: the search for a valid target. *Neurosurgery* 2007, 61(1):1-11.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 9. Houeto JL, Karachi C, Mallet L, Pillon B, Yelnik J, Mesnage V et al. Tourette's syndrome and deep brain
4 stimulation. *J Neurol Neurosurg Psychiatry* 2005, 76(7):992-995.
- 5
6
7 10. Visser-Vandewalle V. DBS in tourette syndrome: rationale, current status and future prospects. *Acta*
8 *Neurochir Suppl* 2007, 97(Pt 2):215-222.
- 9
10
11 11. Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the
12 laboratory to the clinic. *Nat Neurosci* 2007, 10(9):1116-1124.
- 13
14
15 12. Priori A, Foffani G, Pesenti A, Tamma F, Bianchi AM, Pellegrini M et al. Rhythm-specific
16 pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol* 2004, 189(2):369-
17 379.
- 18
19
20
21 13. Raz A, Vaadia E, Bergman H. Firing patterns and correlations of spontaneous discharge of pallidal
22 neurons in the normal and the tremulous 1-methyl-4-phenyl-1, 2,3,6- tetrahydropyridine vervet model of
23 parkinsonism [In Process Citation]. *J Neurosci* 2000, 20(22):8559-71.
- 24
25
26
27 14. Sharott A, Magill PJ, Harnack D, Kupsch A, Meissner W, Brown P. Dopamine depletion increases the
28 power and coherence of beta-oscillations in the cerebral cortex and subthalamic nucleus of the awake rat.
29 *Eur J Neurosci* 2005, 21(5):1413-1422.
- 30
31
32
33 15. Gatev P, Darbin O, Wichmann T. Oscillations in the basal ganglia under normal conditions and in
34 movement disorders. *Mov Disord* 2006, 21(10):1566-1577.
- 35
36
37 16. Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and
38 pathophysiology. *Neuron* 2006, 52(1):155-168.
- 39
40
41 17. Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks,
42 models and treatments. *Trends Neurosci* 2007, 30(7):357-364.
- 43
44
45 18. Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes
46 the firing pattern of pallidal neurons. *J Neurosci* 2003, 23(5):1916-1923.
- 47
48
49 19. Garcia L, Audin J, D'Alessandro G, Bioulac B, Hammond C. Dual effect of high-frequency stimulation on
50 subthalamic neuron activity. *J Neurosci* 2003, 23(25):8743-8751.
- 51
52
53 20. Garcia L, D'Alessandro G, Fernagut PO, Bioulac B, Hammond C. The impact of high frequency
54 stimulation parameters on the pattern of discharge of subthalamic neurons. *J Neurophysiol* 2005.
- 55
56
57 21. Bolam JP, Hanley JJ, Booth PA, Bevan MD. Synaptic organisation of the basal ganglia. *J Anat* 2000,
58 196(Pt 4):527-42.
- 59
60

- 1
- 2
- 3 22. Luscher C, Nicoll RA, Malenka RC, Muller D. Synaptic plasticity and dynamic modulation of the
- 4 postsynaptic membrane. *Nat Neurosci* 2000, 3(6):545-550.
- 5
- 6
- 7 23. Wallace BA, Ashkan K, Heise CE, Foote KD, Torres N, Mitrofanis J et al. Survival of midbrain
- 8 dopaminergic cells after lesion or deep brain stimulation of the subthalamic nucleus in MPTP-treated
- 9 monkeys. *Brain* 2007, 130(Pt 8):2129-2145.
- 10
- 11
- 12
- 13 24. Tai CH, Boraud T, Bezard E, Bioulac B, Gross C, Benazzouz A. Electrophysiological and metabolic
- 14 evidence that high-frequency stimulation of the subthalamic nucleus bridles neuronal activity in the
- 15 subthalamic nucleus and the substantia nigra reticulata. *FASEB J* 2003, 17(13):1820-1830.
- 16
- 17
- 18
- 19 25. Meissner W, Leblois A, Hansel D, Bioulac B, Gross CE, Benazzouz A et al. Subthalamic high frequency
- 20 stimulation resets subthalamic firing and reduces abnormal oscillations. *Brain* 2005, 128(Pt 10):2372-
- 21 2382.
- 22
- 23
- 24
- 25 26. Filali M, Hutchison WD, Palter VN, Lozano AM, Dostrovsky JO. Stimulation-induced inhibition of
- 26 neuronal firing in human subthalamic nucleus. *Exp Brain Res* 2004, 156(3):274-281.
- 27
- 28
- 29 27. Welter ML, Houeto JL, Bonnet AM, Bejjani PB, Mesnage V, Dormont D et al. Effects of high-frequency
- 30 stimulation on subthalamic neuronal activity in parkinsonian patients. *Arch Neurol* 2004, 61(1):89-96.
- 31
- 32
- 33 28. McIntyre CC, Grill WM, Sherman DL, Thakor NV. Cellular effects of deep brain stimulation: model-
- 34 based analysis of activation and inhibition. *J Neurophysiol* 2004, 91(4):1457-1469.
- 35
- 36
- 37 29. Chomiak T, Hu B. Axonal and somatic filtering of antidromically evoked cortical excitation by simulated
- 38 deep brain stimulation in rat brain. *J Physiol* 2007, 579(Pt 2):403-412.
- 39
- 40
- 41 30. Montgomery EB, Jr. Effects of GPi stimulation on human thalamic neuronal activity. *Clin Neurophysiol*
- 42 2006, 117(12):2691-2702.
- 43
- 44
- 45 31. Canteras NS, Shammah-Lagnado SJ, Silva BA, Ricardo JA. Afferent connections of the subthalamic
- 46 nucleus: a combined retrograde and anterograde horseradish peroxidase study in the rat. *Brain Res* 1990,
- 47 513(1):43-59.
- 48
- 49
- 50
- 51 32. Li S, Arbuthnott GW, Jutras MJ, Goldberg JA, Jaeger D. Resonant antidromic cortical circuit activation as
- 52 a consequence of high-frequency subthalamic deep-brain stimulation. *J Neurophysiol* 2007.
- 53
- 54 33. Baker KB, Montgomery EB, Jr., Rezai AR, Burgess R, Luders HO. Subthalamic nucleus deep brain
- 55 stimulus evoked potentials: physiological and therapeutic implications. *Mov Disord* 2002, 17(5):969-983.
- 56
- 57
- 58 34. Cowan RL, Wilson CJ. Spontaneous firing patterns and axonal projections of single corticostriatal
- 59 neurons in the rat medial agranular cortex. *J Neurophysiol* 1994, 71(1):17-32.
- 60

- 1
2
3 35. Sadek AR, Magill PJ, Bolam JP. A single-cell analysis of intrinsic connectivity in the rat globus pallidus.
4
5 J Neurosci 2007, 27(24):6352-6362.
6
7 36. Maurice N, Thierry AM, Glowinski J, Deniau JM. Spontaneous and evoked activity of substantia nigra
8
9 pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. J Neurosci 2003,
10
11 23(30):9929-9936.
12
13 37. Mailly P, Charpier S, Menetrey A, Deniau JM. Three-dimensional organization of the recurrent axon
14
15 collateral network of the substantia nigra pars reticulata neurons in the rat. J Neurosci 2003, 23(12):5247-
16
17 5257.
18
19 38. Hammond C, Rouzair-Dubois B, Féger J, Jackson A, Crossman AR. Anatomical and
20
21 electrophysiological studies on the reciprocal projections between the subthalamic nucleus and nucleus
22
23 tegmenti pedunculopontinus in the rat. Neuroscience 1983, 9(1):41-52.
24
25 39. Florio T, Scarnati E, Confalone G, Minchella D, Galati S, Stanzione P et al. High-frequency stimulation
26
27 of the subthalamic nucleus modulates the activity of pedunculopontine neurons through direct activation
28
29 of excitatory fibres as well as through indirect activation of inhibitory pallidal fibres in the rat. Eur J
30
31 Neurosci 2007, 25(4):1174-1186.
32
33 40. Kita H, Tachibana Y, Nambu A, Chiken S. Balance of monosynaptic excitatory and disynaptic inhibitory
34
35 responses of the globus pallidus induced after stimulation of the subthalamic nucleus in the monkey. J
36
37 Neurosci 2005, 25(38):8611-8619.
38
39 41. Follett KA. Comparison of pallidal and subthalamic deep brain stimulation for the treatment of levodopa-
40
41 induced dyskinesias. Neurosurg Focus 2004, 17(1):E3.
42
43 42. Bar-Gad I, Elias S, Vaadia E, Bergman H. Complex locking rather than complete cessation of neuronal
44
45 activity in the globus pallidus of a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primate in
46
47 response to pallidal microstimulation. J Neurosci 2004, 24(33):7410-7419.
48
49 43. Degos B, Deniau JM, Thierry AM, Glowinski J, Pezard L, Maurice N. Neuroleptic-induced catalepsy:
50
51 electrophysiological mechanisms of functional recovery induced by high-frequency stimulation of the
52
53 subthalamic nucleus. J Neurosci 2005, 25(33):7687-7696.
54
55 44. Lee KH, Chang SY, Roberts DW, Kim U. Neurotransmitter release from high-frequency stimulation of
56
57 the subthalamic nucleus. J Neurosurg 2004, 101(3):511-517.
58
59
60

- 1
- 2
- 3 45. Galati S, Mazzone P, Fedele E, Pisani A, Peppe A, Pierantozzi M et al. Biochemical and
- 4
- 5 electrophysiological changes of substantia nigra pars reticulata driven by subthalamic stimulation in
- 6
- 7 patients with Parkinson's disease. *Eur J Neurosci* 2006, 23(11):2923-2928.
- 8
- 9 46. Maltete D, Jodoin N, Karachi C, Houeto JL, Navarro S, Cornu P et al. Subthalamic stimulation and
- 10
- 11 neuronal activity in the substantia nigra in Parkinson's disease. *J Neurophysiol* 2007, 97(6):4017-4022.
- 12
- 13 47. Hammond C, Deniau JM, Rizk A, Feger J. Electrophysiological demonstration of an excitatory
- 14
- 15 subthalamonigral pathway in the rat. *Brain Res* 1978, 151(2):235-244.
- 16
- 17 48. Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and
- 18
- 19 external pallidum in basal ganglia circuitry. *Brain Res Rev* 1995, 20(1):128-154.
- 20
- 21 49. Charara A, Smith Y, Parent A. Glutamatergic inputs from the pedunculopontine nucleus to midbrain
- 22
- 23 dopaminergic neurons in primates: Phaseolus vulgaris-leucoagglutinin anterograde labeling combined
- 24
- 25 with postembedding glutamate and GABA immunohistochemistry. *J Comp Neurol* 1996, 364(2):254-266.
- 26
- 27 50. Temel Y, Visser-Vandewalle V, Kaplan S, Kozan R, Daemen MA, Blokland A et al. Protection of nigral
- 28
- 29 cell death by bilateral subthalamic nucleus stimulation. *Brain Res* 2006, 1120(1):100-105.
- 30
- 31 51. Moro E, Scerrati M, Romito LM, Roselli R, Tonali P, Albanese A. Chronic subthalamic nucleus
- 32
- 33 stimulation reduces medication requirements in Parkinson's disease. *Neurology* 1999, 53(1):85-90.
- 34
- 35 52. Lacombe E, Carcenac C, Boulet S, Feuerstein C, Bertrand A, Poupard A et al. High-frequency stimulation
- 36
- 37 of the subthalamic nucleus prolongs the increase in striatal dopamine induced by acute 1-3,4-
- 38
- 39 dihydroxyphenylalanine in dopaminergic denervated rats. *Eur J Neurosci* 2007, 26(6):1670-1680.
- 40
- 41 53. Bunney BS, Aghajanian GK, Roth RH. Comparison of effects of L-dopa, amphetamine and apomorphine
- 42
- 43 on firing rate of rat dopaminergic neurones. *Nat New Biol* 1973, 245(143):123-125.
- 44
- 45 54. Benazzouz A, Gao D, Ni Z, Benabid AL. High frequency stimulation of the STN influences the activity of
- 46
- 47 dopamine neurons in the rat. *Neuroreport* 2000, 11(7):1593-1596.
- 48
- 49 55. Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D et al. Bilateral deep brain stimulation
- 50
- 51 of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain* 2007.
- 52
- 53 56. Hariz MI, Krack P, Alesch F, Augustinsson LE, Bosch A, Ekberg R et al. Multicentre European study of
- 54
- 55 thalamic stimulation for Parkinsonian tremor, a 6-year follow-up. *J Neurol Neurosurg Psychiatry* 2007.
- 56
- 57 57. Deuschl G, Bergman H. Pathophysiology of nonparkinsonian tremors. *Mov Disord* 2002, 17 Suppl 3:S41-
- 58
- 59 S48.
- 60

- 1
2
3 58. Anderson T, Hu B, Pittman Q, Kiss ZH. Mechanisms of deep brain stimulation: an intracellular study in
4 rat thalamus. *J Physiol* 2004, 559(Pt 1):301-313.
5
6
7 59. Anderson TR, Hu B, Iremonger K, Kiss ZH. Selective attenuation of afferent synaptic transmission as a
8 mechanism of thalamic deep brain stimulation-induced tremor arrest. *J Neurosci* 2006, 26(3):841-850.
9
10
11 60. Lozano AM, Kumar R, Gross RE, Giladi N, Hutchison WD, Dostrovsky JO et al. Globus pallidus internus
12 pallidotomy for generalized dystonia. *Mov Disord* 1997, 12(6):865-870.
13
14
15 61. Wichmann T, Bergman H, Starr PA, Subramanian T, Watts RL, DeLong MR. Comparison of MPTP-
16 induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia
17 nigra pars reticulata in primates. *Exp Brain Res* 1999, 125(4):397-409.
18
19
20
21 62. Zhuang P, Li Y, Hallett M. Neuronal activity in the basal ganglia and thalamus in patients with dystonia.
22 *Clin Neurophysiol* 2004, 115(11):2542-2557.
23
24
25 63. Tang JK, Moro E, Mahant N, Hutchison WD, Lang AE, Lozano AM et al. Neuronal firing rates and
26 patterns in the globus pallidus internus of patients with cervical dystonia differ from those with
27 Parkinson's disease. *J Neurophysiol* 2007, 98(2):720-729.
28
29
30
31 64. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B. Treatment of DYT1-generalised dystonia by
32 stimulation of the internal globus pallidus. *Lancet* 2000, 355(9222):2220-2221.
33
34
35 65. Benabid AL, Koudsie A, Benazzouz A, Vercueil L, Fraix V, Chabardes S et al. Deep brain stimulation of
36 the corpus luyisi (subthalamic nucleus) and other targets in Parkinson's disease. Extension to new
37 indications such as dystonia and epilepsy. *J Neurol* 2001, 248 Suppl 3:III37-III47.
38
39
40
41 66. Vercueil L, Pollak P, Fraix V, Caputo E, Moro E, Benazzouz A et al. Deep brain stimulation in the
42 treatment of severe dystonia. *J Neurol* 2001, 248(8):695-700.
43
44
45 67. Kupsch A, Benecke R, Muller J, Trottenberg T, Schneider GH, Poewe W et al. Pallidal deep-brain
46 stimulation in primary generalized or segmental dystonia. *N Engl J Med* 2006, 355(19):1978-1990.
47
48
49
50 68. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Lagrange C, Yelnik J et al. Bilateral, pallidal, deep-
51 brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. *Lancet Neurol*
52 2007, 6(3):223-229.
53
54
55 69. Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus
56 on the activity of thalamic neurons in the awake monkey. *J Neurophysiol* 2003, 89(2):1150-1160.
57
58
59
60

- 1
2
3 70. Baxter LR, Jr., Phelps ME, Mazziotta JC, Guze BH, Schwartz JM, Selin CE. Local cerebral glucose
4 metabolic rates in obsessive-compulsive disorder. A comparison with rates in unipolar depression and in
5 normal controls. *Arch Gen Psychiatry* 1987, 44(3):211-218.
6
7
8
9 71. Swedo SE, Schapiro MB, Grady CL, Cheslow DL, Leonard HL, Kumar A et al. Cerebral glucose
10 metabolism in childhood-onset obsessive-compulsive disorder. *Arch Gen Psychiatry* 1989, 46(6):518-523.
11
12
13 72. Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in
14 obsessive-compulsive disorder. *Br J Psychiatry Suppl* 1998,(35):26-37.
15
16
17 73. Guehl D, Benazzouz A, Aouizerate B, Cuny E, Rotge JY, Rougier A et al. Neuronal Correlates of
18 Obsessions in the Caudate Nucleus. *Biol Psychiatry* 2007.
19
20
21 74. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of
22 internal capsules in patients with obsessive-compulsive disorder. *Lancet* 1999, 354(9189):1526.
23
24
25 75. Van Kuyck K., Gabriels L, Cosyns P, Arckens L, Sturm V, Rasmussen S et al. Behavioural and
26 physiological effects of electrical stimulation in the nucleus accumbens: a review. *Acta Neurochir Suppl*
27 2007, 97(Pt 2):375-391.
28
29
30
31 76. McCracken CB, Grace AA. High-frequency deep brain stimulation of the nucleus accumbens region
32 suppresses neuronal activity and selectively modulates afferent drive in rat orbitofrontal cortex in vivo. *J*
33 *Neurosci* 2007, 27(46):12601-12610.
34
35
36
37 77. Ranck JB. Which elements are excited in electrical stimulation of mammalian central nervous system: a
38 review. *Brain Res* 1975, 98(3):417-440.
39
40
41 78. Nowak LG, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray
42 matter. I. Evidence from chronaxie measurements. *Exp Brain Res* 1998, 118(4):477-488.
43
44
45 79. Windels F, Bruet N, Poupard A, Feuerstein C, Bertrand A, Savasta M. Influence of the frequency
46 parameter on extracellular glutamate and gamma-aminobutyric acid in substantia nigra and globus
47 pallidus during electrical stimulation of subthalamic nucleus in rats. *J Neurosci Res* 2003, 72(2):259-267.
48
49
50
51 80. Windels F, Carcenac C, Poupard A, Savasta M. Pallidal origin of GABA release within the substantia
52 nigra pars reticulata during high-frequency stimulation of the subthalamic nucleus. *J Neurosci* 2005,
53 25(20):5079-5086.
54
55
56
57 81. Lee KH, Kristic K, van HR, Hitti FL, Blaha C, Harris B et al. High-frequency stimulation of the
58 subthalamic nucleus increases glutamate in the subthalamic nucleus of rats as demonstrated by in vivo
59 enzyme-linked glutamate sensor. *Brain Res* 2007, 1162:121-129.
60

- 1
2
3 82. Meissner W, Guigoni C, Cirilli L, Garret M, Bioulac BH, Gross CE et al. Impact of chronic subthalamic
4 high-frequency stimulation on metabolic basal ganglia activity: a 2-deoxyglucose uptake and cytochrome
5 oxidase mRNA study in a macaque model of Parkinson's disease. *Eur J Neurosci* 2007, 25(5):1492-1500.
6
7
8
9 83. Oueslati A, Sgambato-Faure V, Melon C, Kachidian P, Gubellini P, Amri M et al. High-frequency
10 stimulation of the subthalamic nucleus potentiates L-DOPA-induced neurochemical changes in the
11 striatum in a rat model of Parkinson's disease. *J Neurosci* 2007, 27(9):2377-2386.
12
13
14
15

16 Legends

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

18
19
20
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
24 nuclei of the extrastriatal network and motor cortical areas are directly affected by STN-DBS.
25
26 The striatal network is indirectly affected via the modulation of dopaminergic neurons of the
27 SNc. When antidromic spikes propagate back to a structure, they may invade somas and axon
28 collaterals and thus activate other projection neurons and local interneurons when they exist
29 (insets show simplified cortical⁷⁶ and GPe networks).
30
31
32
33
34
35
36
37
38
39
40
41

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

43
44 Antidromic responses in (A) STN neurons in response to STN-HFS (note IS spike at t=120
45 ms, middle and IS-SD break, right) (Garcia et al, unpublished figure) (B) Motor cortical
46 neurons in response to STN-DBS (arrow head indicates collision, right)³², (C) GPe neurons in
47 response to STN-DBS (Ammari et al, unpublished data) (D) SNr neurons in response to STN-
48 DBS (note collision, bottom trace, right)³⁶, (E) Vop thalamic neurons in response to GPi-DBS
49 (post-stimulus raster plot, top; histogram, bottom; antidromic spikes, right)³⁰.
50
51
52
53
54
55
56
57
58
59
60

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

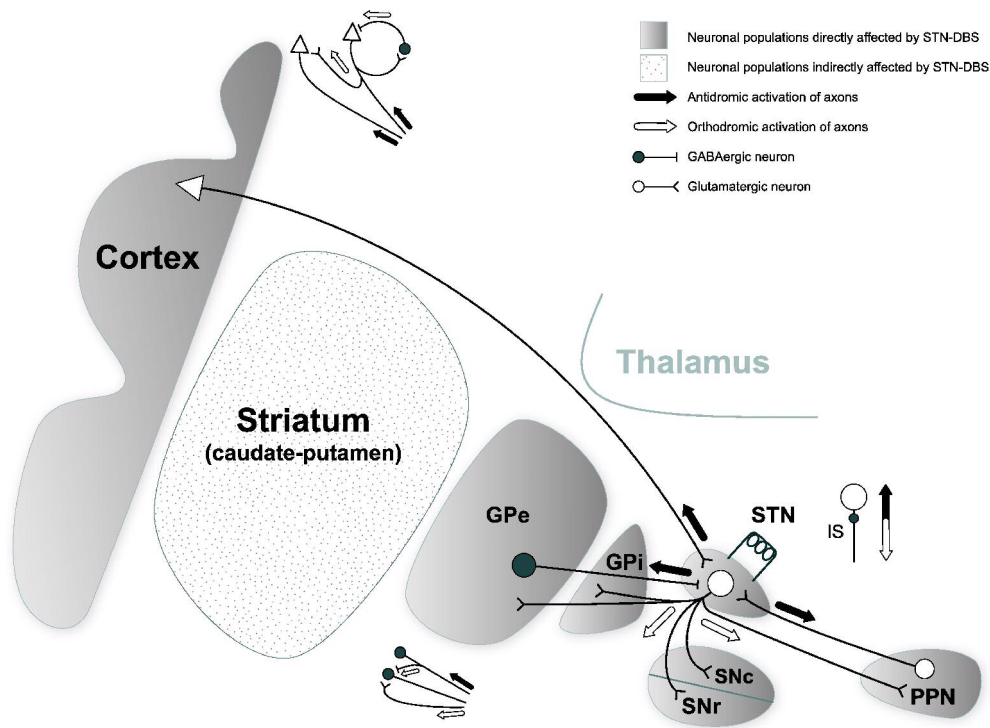


Figure 1: STN and the striatal and extrastriatal networks STN-DBS preferentially activates axons thus generating spikes that propagate in the antidromic (towards STN, motor cortex, GPe & PPN somas) and orthodromic (towards GPe, GPI, SNr, SNc, PPN) directions. Passing fibers can also be activated. As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

192x141mm (600 x 600 DPI)

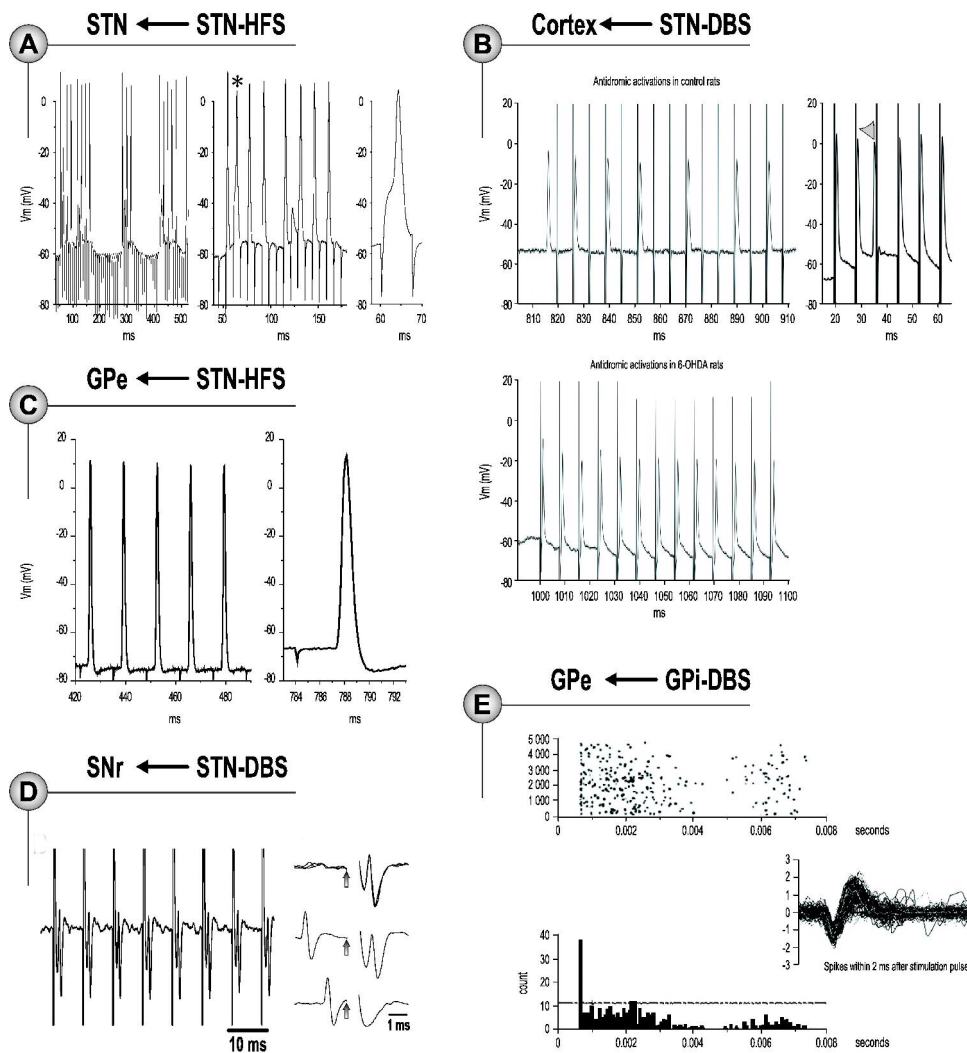


Figure 2 DBS-driven antidromic spikes Antidromic responses in (A) STN neurons in response to STN-HFS (note IS spike at $t=120$ ms, middle and IS-SD break, right) (Garcia et al, unpublished figure) (B) Motor cortical neurons in response to STN-DBS (arrow head indicates collision, right)³², (C) GPe neurons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

205x220mm (600 x 600 DPI)

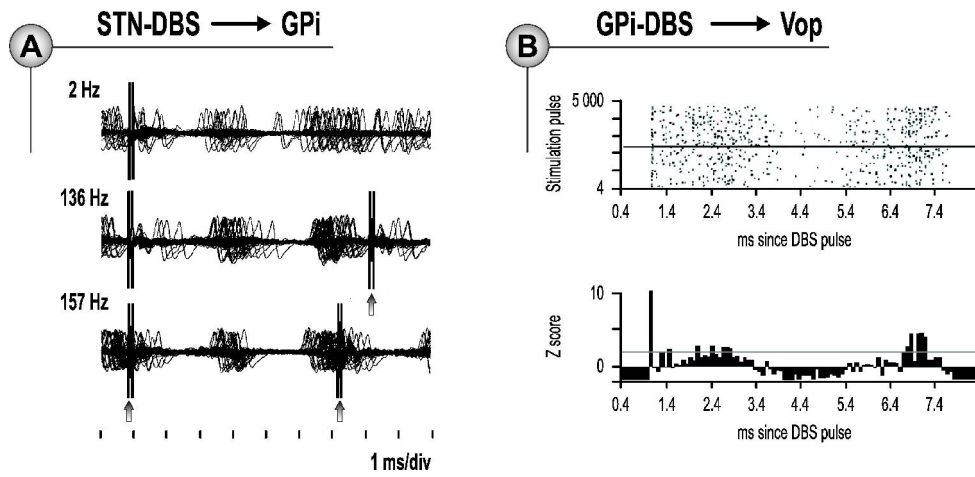


Figure 3: DBS-driven orthodromic responses Orthodromic responses of (A) GPI neurons in response to STN-DBS (complex sequence of excitation-inhibition-excitation)¹⁸, (B) Vop thalamic neurons in response to GPI-DBS (antidromic activation followed by a complex sequence of excitation-inhibition-excitation, post stimulus raster, top and histogram, bottom)³⁰.

181x83mm (600 x 600 DPI)

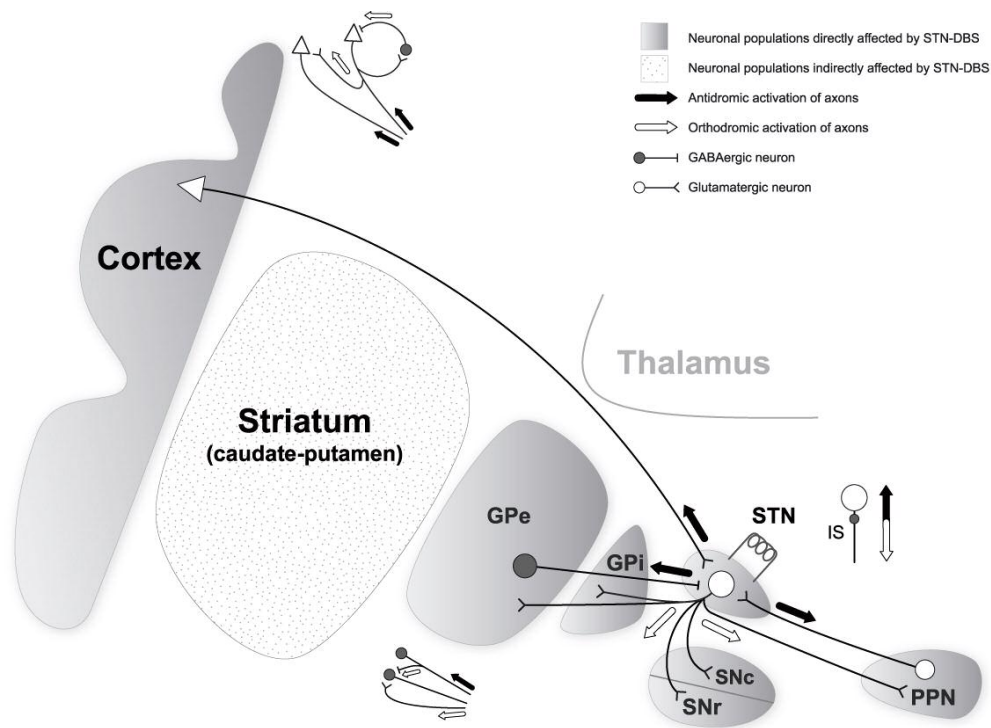


Figure 1: STN and the striatal and extrastriatal networks STN-DBS preferentially activates axons thus generating spikes that propagate in the antidromic (towards STN, motor cortex, GPe & PPN somas) and orthodromic (towards GPe, GPi, SNr, SNc, PPN) directions. Passing fibers can also be activated. As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

192x141mm (150 x 150 DPI)

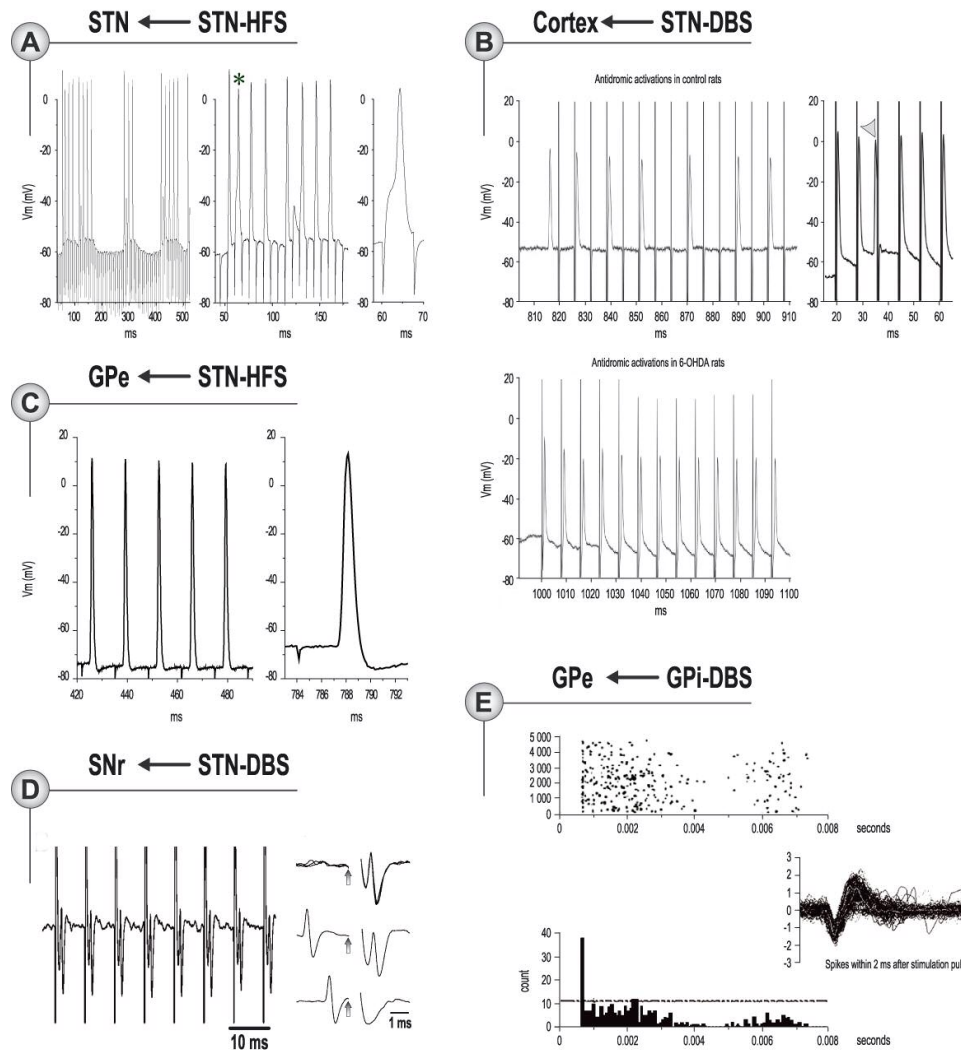


Figure 2 DBS-driven antidromic spikes Antidromic responses in (A) STN neurons in response to STN-HFS (note IS spike at $t=120$ ms, middle and IS-SD break, right) (Garcia et al, unpublished figure) (B) Motor cortical neurons in response to STN-DBS (arrow head indicates collision, right)³², (C) GPe neurons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

205x220mm (150 x 150 DPI)

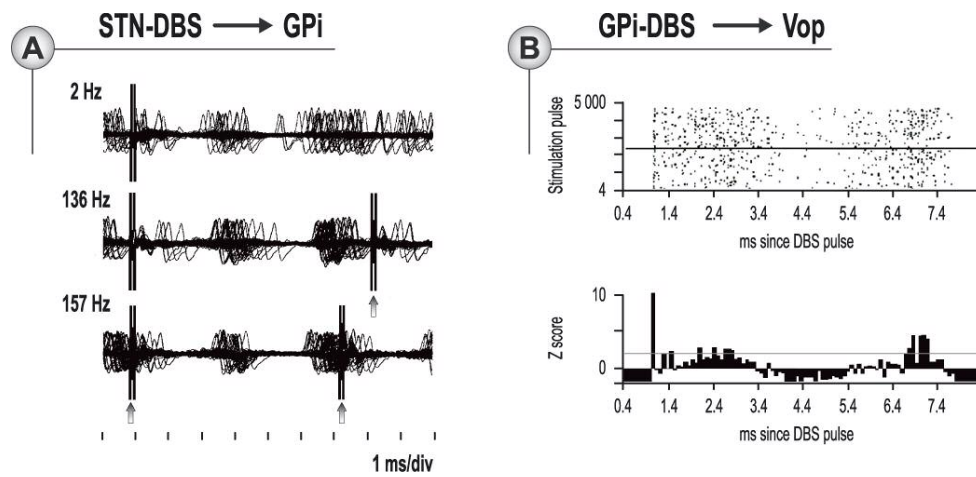


Figure 3: DBS-driven orthodromic responses Orthodromic responses of (A) GPI neurons in response to STN-DBS (complex sequence of excitation-inhibition-excitation)¹⁸, (B) Vop thalamic neurons in response to GPI-DBS (antidromic activation followed by a complex sequence of excitation-inhibition-excitation, post stimulus raster, top and histogram, bottom)³⁰.

182x83mm (150 x 150 DPI)