High-frequency stimulation in Parkinson's disease: more or less?

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Deep-brain stimulation at high frequency is now considered the most effective neurosurgical therapy for movement disorders. An electrode is chronically implanted in a particular area of the brain and, when continuously stimulated, it significantly alleviates motor symptoms. In Parkinson's disease, common target nuclei of high-frequency stimulation (HFS) are ventral thalamic nuclei and basal ganglia nuclei, such as the internal segment of the pallidum and the subthalamic nucleus (STN), with a preference for the STN in recent years. Two fundamental mechanisms have been proposed to underlie the beneficial effects of HFS: silencing or excitation of STN neurons. Relying on recent experimental data, we suggest that both are instrumental: HFS switches off a pathological disrupted activity in the STN (a 'less' mechanism) and imposes a new type of discharge in the upper gamma-band frequency that is endowed with beneficial effects (a 'more' mechanism). The intrinsic capacity of basal ganglia and particular STN neurons to generate oscillations and shift rapidly from a physiological to a pathogenic pattern is pivotal in the operation of these circuits in health and disease.

Introduction

Chronic high-frequency stimulation (HFS) of the brain, also referred as to deep-brain stimulation, is becoming increasingly important in the treatment of movement disorders. In the case of Parkinson's disease, which results from the degeneration of the dopaminergic neurons of the substantia nigra, HFS of the subthalamic nucleus (STN) (Figure 1) is now a widely used neurosurgical therapy because it markedly improves motor symptoms (bradykinesia, rigidity and tremor) and reduces medication needs [1–3]. The ideal candidate patient for HFS should have a preserved good L-dopa response but long-term treatment side effects, such as motor fluctuations and dyskinesias. Congruently, dopaminergic medication can be reduced up to 50% during STN-HFS. In both patients and animal models of Parkinson's disease, STN neurons have a pathological activity characterized by loss of specificity in receptive fields, irregular discharge with a tendency towards bursting, and abnormal synchronization [4–8].

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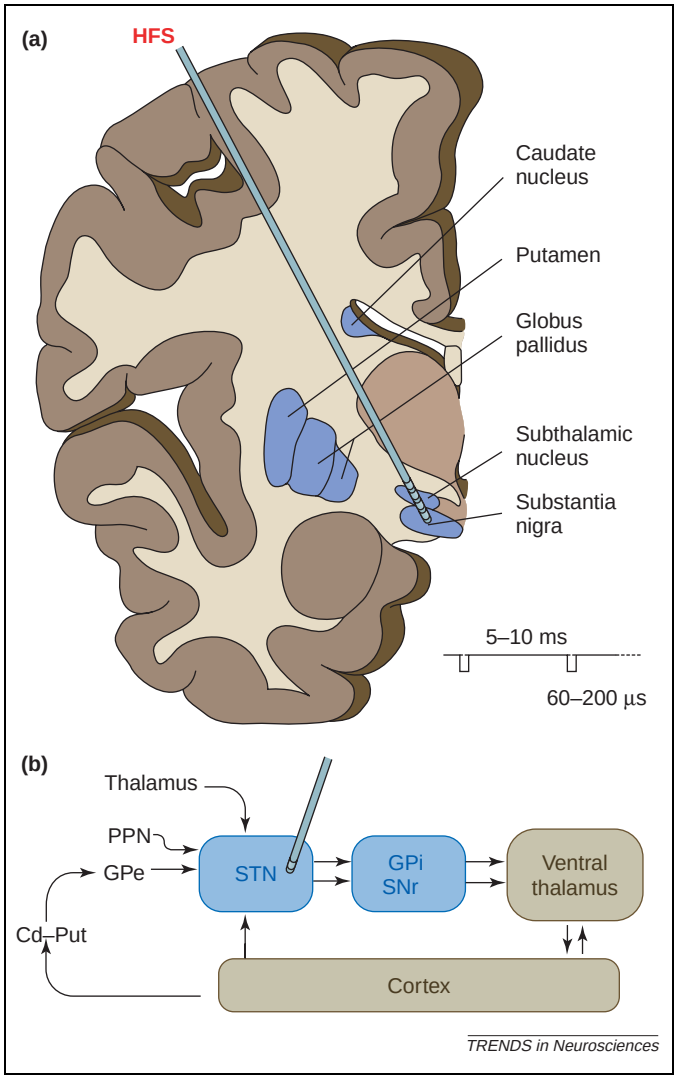

Figure 1. Schematic representation of the basal ganglia nuclei and a high-frequency stimulation (HFS) electrode implanted in the subthalamic nucleus (STN). **(a)** The basal ganglia are interconnected nuclei: the caudate nucleus and putamen (Cd–Put), the globus pallidus (external GPe and internal GPi segments), the STN and the substantia nigra (SN). HFS is applied to the STN in pulses of 60–200 μs every 5–10 ms. **(b)** Basal ganglia are included in a cortical–basal ganglia–thalamocortical loop. STN controls the output nuclei of the basal ganglia [the GPi and pars reticulata of the SN (SNr)]. STN receives afferents from the basal ganglia (GPe) and from structures external to the basal ganglia [cortex, parafascicular nucleus of the thalamus and pedunculopontine nucleus (PPN)]. The direct striatonigral pathway is not directly controlled by STN-HFS and is omitted from this figure.

 0166-2236/$ - see front matter doi:10.1016/j.tins.2005.02.005

The observations that STN activity is disorganized in the Parkinsonian state and that lesion or chemical inactivation of STN neurons ameliorate motor symptoms led to the hypothesis that STN stimulation at high frequency silences STN neurons and, by eliminating a pathological activity or a pathological pattern, alleviates the symptoms [9–13]. However, this 'less' hypothesis raises several issues that have not been clarified. Electrical stimulation in the CNS usually causes, rather than blocks, activity of axons [14], and STN neurons can discharge high-frequency spikes [15], casting doubt on the silencing hypothesis. Other electrophysiological, pharmacological and metabolic studies raise another possibility, which we refer to as the 'more' hypothesis: HFS not only suppresses the pathological STN activity but also imposes a new activity on STN neurons. This is not simply excitation (spikes evoked among spontaneous ones) but rather total replacement of the pathological activity of STN neurons by a new HFS-driven pattern that can influence the target neurons of the STN – that is, the output structures of the basal ganglia. This article summarizes cellular and imaging results obtained in different preparations and discusses the functional role of STN-HFS in the basal ganglia network.

HFS parameters

In patients, STN-HFS is an extracellular, cathodic, monopolar 24-hours-a-day stimulation delivered through large four-contact electrodes. Such stimulation induces an electrical field that spreads and depolarizes neighboring membranes – those of afferent axons, cell bodies, efferent axons and axons surrounding the STN – depending on neuronal element orientation and position in the field, and on stimulation parameters [16,17].

Comparison of HFS in patients, in animals and in vitro

Optimal clinical results are obtained on an empirical basis using pulses of 60–200 μs duration and 1–5 V amplitude, delivered in the STN at 120–180 Hz (Figure 1). Frequency is the most important parameter because stimulation at 5–10 Hz worsens parkinsonism and no significant improvement is observed between 10 Hz and 50 Hz [3,18]. Pulse frequency and pulse width are parameters that remain constant whichever electrode and recording configuration is used. By contrast, comparison of pulse amplitude between different *in vivo* and *in vitro* studies is complicated by differences of the surrounding medium and the surface area of electrode contact. The contacts of the electrode used in the clinic are large compared with those generally used in rat tissue *in vivo* and *in vitro*. As a result, to deliver similar current density at the electrode contact, we should apply less current in the rat STN than in the human STN. However, because the rat STN is much smaller, a smaller-tipped electrode with the same current density could produce a comparable effect in terms of percentage of neurons activated.

Neural elements activated at low versus high frequency

Axons represent the most excitable components of neurons [19,20] and are activated by low and high frequencies of stimulation. By contrast, the postsynaptic responses resulting from activation of afferent axons vary according to the frequency and duration of the stimulation. Low-frequency stimulation of the STN (STN-LFS, 0.1–30.0 Hz) depolarizes glutamatergic and GABAergic synaptic terminals close to the stimulating electrode and evokes inhibitory and excitatory postsynaptic potentials (IPSPs and EPSPs, respectively) and spikes (Table 1). In general, these postsynaptic responses show plasticity and vary with the frequency and duration of stimulation. For example, glutamate-mediated EPSPs do not follow long-term 130-Hz stimulation of the STN [21], and the amplitude of GABA-dependent IPSPs diminishes during repetitive stimulation in other networks [22].

Techniques and preparations employed to study the mechanisms of HFS include electrophysiological techniques (extracellular recordings *in vivo* or intracellular recordings *in vitro*), measurement of neurotransmitter release *in vivo*, post-mortem immunohistochemistry of a metabolic marker, and imaging studies *in vivo*. Each approach has its advantages and limitations, and comparison of their results should be of great interest. However, fundamental procedures must be respected. HFS must be tested at therapeutic ($\geq$100 Hz) and non-therapeutic ($<$50 Hz) frequencies for comparison, and it must be applied for at least minutes to mimic its clinical use (Table 2).

Table 1. LFS parameters used to analyze the responses of STN neurons during LFS[a,b]

Stimulating electrode	LFS duration	Pulse frequency (Hz)	Pulse width (μs)	Pulse amplitude (μA)	Preparation	Response	Refs
Monopolar	20 s	14	60	2000	Patients	No effect	[25][c]
Monopolar	500 ms	5	200	2–500	Patients	Inhibition	[24][c]
Bipolar	1–2 min	5	50	20–150	Control rats	No effect	[26]
Bipolar	10 s	1–10	60	400	Control and 6-OHDA - anesthetized rats	No effect or inhibition	[27]
Bipolar	100 ms	30–80	NR	0.2–1.0	Slices from control rats	EPSPs	[31]
NR	10 s	10–25	50–100	10–500	Slices from control rat	EPSPs, spikes	[34]
NR	200 ms	20	50–100	10–500	Slices from control rats	EPSPs, IPSPs	[29]
Monopolar	1–2 h	10	90	500	Slices from control and dopamine-depleted rats	EPSPs, spikes	[21]

[a]The upper four rows are from extracellular recordings and the lower four rows are from intracellular recordings.
[b]Abbreviations: 6-OHDA, 6-hydroxydopamine; EPSPs, excitatory postsynaptic potentials; IPSPs, inhibitory postsynaptic potentials; LFS, low-frequency stimulation; NR, not reported; STN, subthalamic nucleus.
[c]Parameters for stimulation through large macroelectrodes.

Table 2. HFS parameters used to analyze the responses of STN neurons during HFS[a,b]

Stimulating electrode	HFS duration	Pulse frequency (Hz)	Pulse width (μs)	Pulse amplitude (μA)	Preparation	Author conclusion	Refs
Monopolar	20 s	140	60	2000	Patients	Inhibition	[25][c]
Monopolar	90–500 ms	100–300	200	75–500	Patients	Inhibition	[24][c]
Bipolar	10 s	130	60	400	Control and 6-OHDA-anesthetized rats	Inhibition	[27]
Bipolar	10–60 s	70–120	NR	0.2–1.0	Slices from control rats	Bursts then inhibition	[31]
NR	0.1–2.0 s	100–140	50–100	10–500	Slices from control rats	Excitation	[29]
Monopolar	1–2 h	80–185	90	500	STN slice from control and dopamine-depleted rats	Dual effect: bursts and inhibition	[21]

[a]Only papers illustrating electrophysiological recordings have been taken into account. The upper three rows are from extracellular recordings and the lower three rows are from intracellular recordings.
[b]Abbreviations: 6-OHDA, 6-hydroxydopamine; HFS, high-frequency stimulation; NR, not reported; STN, subthalamic nucleus.
[c]Parameters for stimulation through large macroelectrodes.

Less

HFS is followed by a period of silence

STN activity was originally recorded immediately after cessation of HFS, when artifacts are no longer present. Such results consistently show a post-stimulus period of reduced neuronal firing followed by the slow recovery of spontaneous activity. HFS at frequencies >50 Hz in the STN of patients undergoing functional stereotactic procedures [23–25], in the STN of rats *in vivo* [26,27] and in rat STN slices *in vitro* [21,28,29] produces a period of neuronal silence of hundreds of milliseconds to tens of seconds (Figure 2a). The transient depression of the persistent Na^+ and T-type Ca^{2+} currents that normally underlie spontaneous activity of STN neurons [15,30] can explain the post-HFS silence [28]. One central limitation of such an approach is that what happens once the stimulation is stopped might be only partly relevant for the actual actions of HFS (i.e. during stimulation). For this reason, recordings were subsequently performed during HFS.

HFS inhibits STN activity

Figure 2b compares extracellular STN recordings during brief STN-HFS in patients off medication and in the murine model of parkinsonism. They all show reduced STN activity [24,25,27]. At 5–14 Hz, STN-LFS evokes inhibition or no response (Table 1, first four rows) but the higher the frequency of stimulation, the higher the percentage of neurons presenting an inhibitory response (Table 2, first three rows). By contrast, intracellular study in slices from control rats reveals a primary period of excitation during a brief HFS [31]. Cells present a tonic activity with few action potential failures, then switch to bursting mode and eventually stop firing. Whether single spikes or spikes within bursts are spontaneous or evoked by the stimuli has not been analyzed. Magarinos-Ascone *et al.* conclude that HFS inhibits STN activity. Histological analysis of the expression of cytochrome oxidase subunit I (CoI) mRNA is an indicator of STN metabolic activity [32] and has the advantage of eliminating the problem of stimulation artifacts. Long-term HFS (130 Hz, 60 μs, lasting for 45 min to 2 h) decreases by ~10–35% expression of CoI mRNA in the stimulated STN of control and lesioned rats, whether anaesthetized or awake [27,33]. By contrast, stimulation at 20 Hz has no effect.

HFS inhibits target neuron activity

STN neurons fire with a pathological pattern in the parkinsonian state and their inactivation can decrease

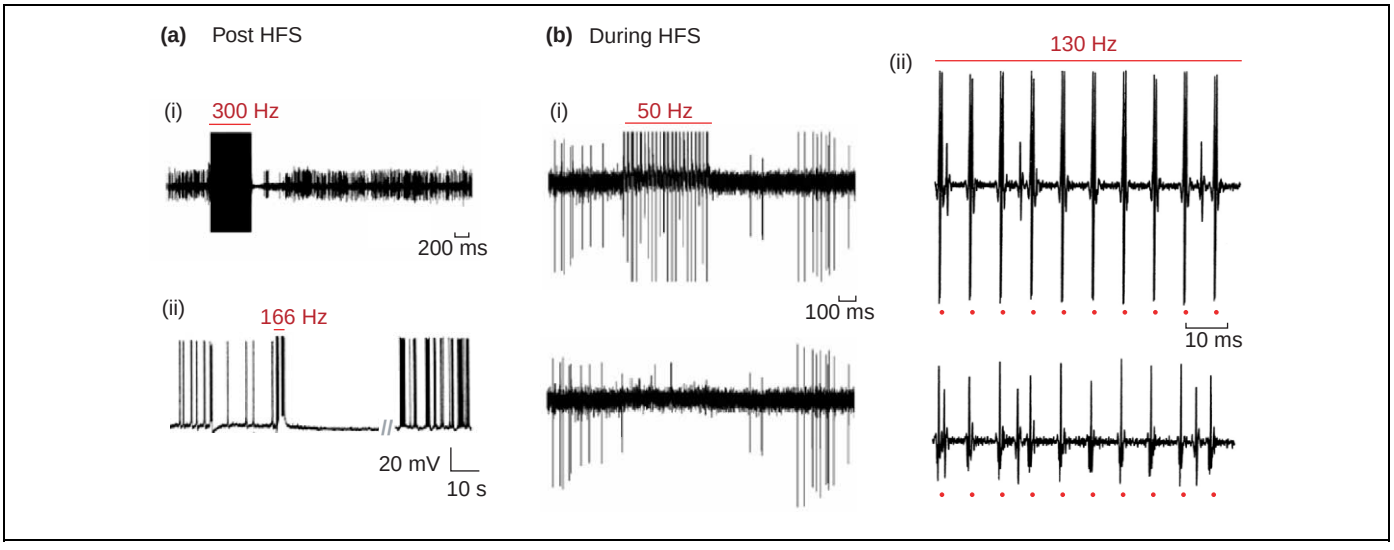

Figure 2. Inhibitory effect of high-frequency stimulation (HFS). **(a)** Decrease of subthalamic nucleus (STN) activity recorded immediately after STN-HFS (i) in patients (extracellular recordings) [23] and (ii) in rat STN slices (whole-cell recordings) [28]. The red bar indicates duration of HFS at the stated frequency. **(b)** Decrease of STN activity during brief STN-HFS (i) in patients [24] and (ii) in rats *in vivo* [27]. Control activity in the STN was regular (15.24 Hz±1.44 Hz) before stimulation and decreased to 7.43 Hz±1.19 Hz during stimulation in 87% of the recorded neurons. Upper traces are recordings before suppression or scale-down of artifacts and bottom traces are recordings after this procedure. Large spikes are artifacts and red dots indicate them in (b,ii).

activity in STN target structures – the globus pallidus (GP) and substantia nigra (SN). Burbaud *et al.* [26] and Tai *et al.* [27] have shown that brief STN-HFS (100–130 Hz, lasting for 20–120 s) in control or lesioned rats *in vivo* either decreases SN pars reticulata (SNr) firing rates or has no effect. In the GP, it causes modest inhibition (12%) in half of the neurons recorded [26].

Shortcomings of the 'less' hypothesis

The silencing hypothesis is based on extracellular recordings during very short periods of HFS (Table 2). One potential problem with studies relying on extracellular recordings is that large stimulus artifacts (of ~2 ms duration), in particular when the stimulation is close to the recording site, preclude detection of possible short latency (~1 ms) action potentials evoked by direct stimulation of nearby cell bodies or axons. This problem is exemplified by results following intranuclear LFS. LFS is commonly used to evoke EPSPs and spikes in intracellular recordings *in vitro*. These evoked spikes have not been observed in extracellular recordings *in vivo* (Table 1), suggesting that artifacts mask them. To solve this problem, artifacts are scaled down using diverse procedures; however, whether these procedures really unmask spikes or only clean recordings should be tested during LFS (Figure 2b).

Proposed mechanisms for the silencing are (i) a direct effect of HFS on STN neuronal membranes (the depolarization block hypothesis) and (ii) 'preferential' activation of GABAergic inhibitory afferents to STN neurons. A depolarizing block means that the membrane is so depolarized that spikes become smaller and smaller and finally can no longer be evoked, owing to inactivation of the voltage-gated Na^+ current. Filali *et al.* [24] and Tai *et al.* [27] have excluded this hypothesis, because STN spike amplitude does not change in the initial part of the train and the firing rate does not increase before activity decreases. Enhancement of GABAergic currents is also unlikely because of the usual failure of inhibition during long-term repetitive stimulation [22]. Although the CoI mRNA results are compatible with inhibition, these observations are conditioned by the possible rapid changes of STN activity once HFS is stopped, and by the fact that HFS-driven activity might need less energy than pathological activity. Finally, the analysis of SN responses to STN-HFS cannot provide direct information about the effect of HFS on STN neurons, owing to the complexity of the intranigral network. In conclusion, there is indeed a reduction of the number of STN spontaneous spikes between stimulation artifacts, but very short-latency evoked spikes close to the artifacts would not be detected in these experiments. Intracellular recordings of STN neuronal activity or extracellular recordings of target neuron responses should enable such spikes to be distinguished from stimulation artifacts, owing to the large amplitude of STN intracellular spikes and the latencies of target cell responses.

More

HFS excites STN neurons

Lee *et al.* [29,34] have reported that STN-HFS involves excitation in rat slices *in vitro* (Table 2). LFS at 20 Hz evokes EPSPs and spikes (Table 1) and HFS at 100–140 Hz increases action potential firing to its maximum (Table 2). Lee *et al.* did not analyze precisely the relationship between spikes and stimuli, or the behavior of spontaneous activity during HFS. Because spikes disappear in the presence of channel blockers, EPSPs and spikes generated during 2 s trains at 100 Hz are proposed to result from the activation of glutamate-mediated transmission.

HFS has a dual effect

In whole-cell recordings from rat STN slices [21], long-term (1–2 h) HFS (80–185 Hz) evokes bursts of spikes (Table 2 and Figure 3a). Detailed analysis shows that within bursts each spike is evoked by a stimulus, although not all stimuli evoke a spike, and spontaneous spikes are absent between stimuli. Therefore, during HFS, the activity of the recorded STN neurons is no longer spontaneous but becomes entirely driven by the stimulation. This new HFS-driven pattern results from direct activation of the STN membrane because it is still present when blockers of glutamate and GABA receptor channels are applied. Neurons respond intermittently (in bursts) to HFS, even though HFS is continuous, owing to intrinsic membrane properties of STN neurons [35]. The membrane is hyperpolarized between bursts probably as a result of Ca^{2+} entry during bursts. Stimuli cannot evoke spikes during these hyperpolarized periods. We propose that HFS at therapeutic parameters has a dual effect: it suppresses spontaneous activity and drives STN neuronal activity (Figure 3a). Interestingly, non-therapeutic LFS (1–10 Hz) evokes EPSPs and spikes at 1–10 Hz and does not suppress spontaneous activity; rather, it has a simple excitatory effect (Table 1).

HFS excites target neurons of the STN (GP and SN)

Stimulation of glutamatergic STN neurons [36] evokes excitatory responses in neurons of the internal GP (GPi) and SN [37–39], but STN stimulation can also elicit sequences of excitation–inhibition owing to the complexity of the network. For example, it can activate polysynaptic GABAergic pathways such as (i) STN–external GP (GPe)–GPi or STN–GPe–SN pathways, (ii) striato–nigral fibers that run in the vicinity of the STN, and (iii) intranigral SNr axon collaterals, via activation of the STN–SNr pathway. STN-HFS in control rats *in vivo* excites 21% of SNr cells and inhibits 79% of them (with a mean latency of 5.0 ± 0.8 ms) [40] (Figure 3b). In monkeys with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), during STN-HFS at a frequency that can alleviate parkinsonian signs (136 Hz or 185 Hz, lasting for 25–35 s), the majority of GPi neurons (85%) respond with a sequence of inhibition–excitation–inhibition–excitation [41]. Peaks of activity occur at 4 ms and 8 ms of latency. The discharge pattern of GPi neurons changes from irregular to regular, tightly correlated with time of the stimulation pulse (Figure 3c). Latencies of the excitatory responses are compatible with activation of subthalamo–nigral [37] or subthalamo–pallidal [42] neurons, thus strongly suggesting that STN-HFS activates output STN neurons, with inhibition resulting from the activation of polysynaptic pathways.

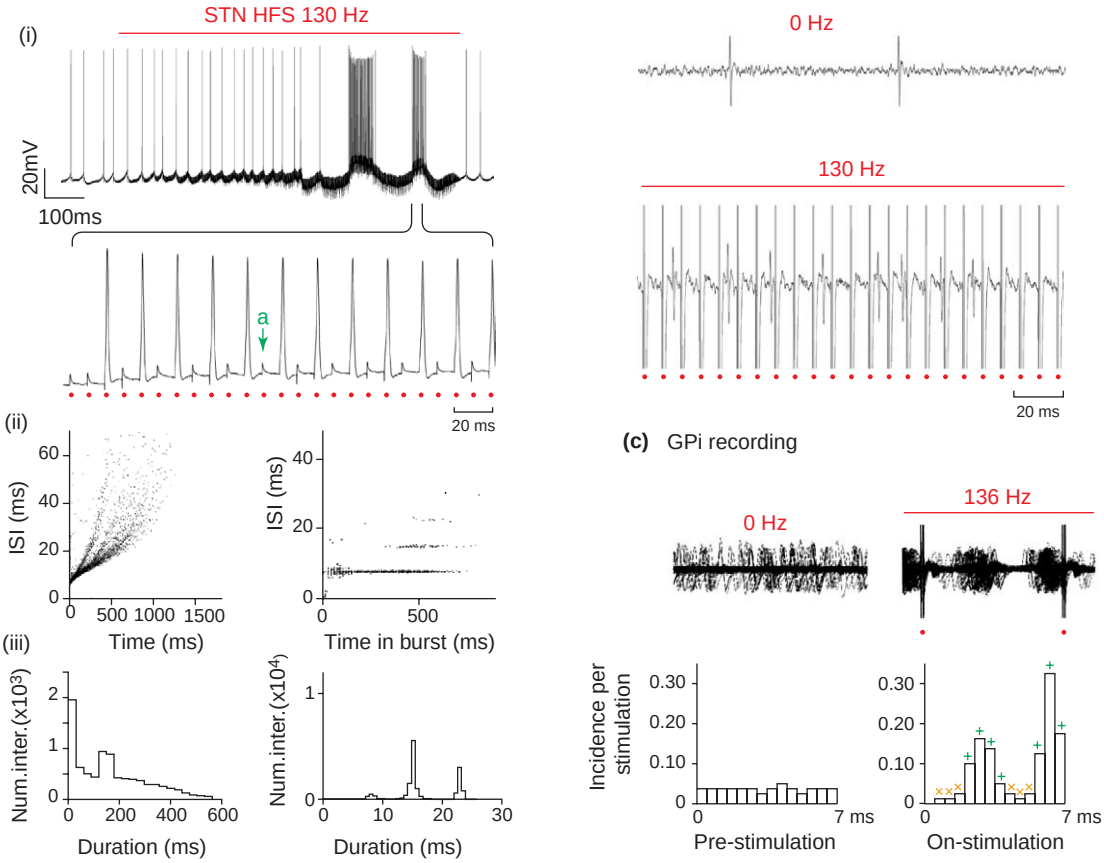

Figure 3. Dual effect of HFS in the STN and excitation of target neurons. **(a)** Dual effect of high-frequency stimulation (HFS) of the subthalamic nucleus (STN) *in vitro*: (i) HFS forces STN neurons to discharge spikes (single or organized in bursts) that are time-locked to the stimulation [21]. The expanded trace shows that some stimuli ('a', a stimulation artifact) do not evoke spikes and others evoke spikes with no detectable latency. Note the absence of spontaneous spikes. (ii) Interspike intervals (ISIs) as a function of time in the recording before HFS (left) and as a function of time of occurrence within a burst during HFS at 130 Hz (right). Note that during HFS all spikes are on average time-locked to one every 2–3 stimuli. (iii) Number of ISIs (Num.inter.) before HFS (left) and within bursts during HFS at 130 Hz (right). **(b,c)** Excitatory responses evoked in target neurons of the STN. (b) Extracellular recordings in SNr in the rat *in vivo* during STN-HFS, showing spikes evoked one every 2–3 stimulations with a mean latency of 3–6 ms [40]. (c) Overlays of 100 sweeps of extracellular recordings in GPi during STN-HFS in MPTP-treated monkeys, showing the regular pattern of the evoked discharge [41]. Below are the post-stimulus histograms reconstructed from successive 7-ms periods before (left) and during (right) HFS. Increases significant at $P<0.01$ are indicated with '+'; decreases significant at $P<0.01$ are indicated with 'x'. Red dots indicate stimulation artifacts.

In patients greatly ameliorated by the stimulation, STN-HFS (pulses at 130–185 Hz, of 60–70 μs duration and 1.5–3.4 V amplitude) increases blood flow, regional cerebral metabolic rates and blood oxygenation [measured using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI)] in the ipsilateral GPe [43–45]. Similarly, in rats *in vivo*, STN-HFS (60–130 Hz) provoked a significant increase of glutamate content in both GPe and SNr, as measured using microdialysis [46,47]. This increase was amplified and remained significant throughout the stimulation period (1 h), with maximal effect 1 h after the end of stimulation. The glutamate concentration increase could correspond to activation of STN neurons, as occurs during their pharmacological activation by carbachol [48]. STN-LFS at 10 Hz has no effect, probably because the increased release of glutamate caused by the relatively small increase in activity (25%) is not detectable.

HFS and striatal dopamine release

STN-HFS can influence the activity of dopaminergic neurons either directly [37,49] or indirectly via collaterals of SNr cells (Figure 4a). Whenever tested, STN-HFS has been found to increase dopamine content or metabolism in the ipsilateral striatum in control and partially dopamine-denervated rats [50,51]. By contrast, HFS of the entopeduncular nucleus has no effect [52]. During the STN-HFS period (130 Hz for 1 h), the ipsilateral extracellular content of dopamine increases by up to 200% in 6-hydroxydopamine lesioned rats bearing partial destruction of the SN pars compacta (SNc) and by less in control rats (168%) [50]. Intraneuron dopamine turnover and tyrosine hydroxylase activity also increase [51]. These results have not been confirmed in patients. Dopamine release is estimated in patients as the density of free D2 receptors in the striatum, measured using the reversible ligand [^{11}C] raclopride in PET experiments. Binding of this tracer is inversely proportional to levels of extracellular dopamine [53]. After a period when the stimulation has been turned off and L-dopa withdrawn, STN-HFS in one side does not induce differences in [^{11}C]raclopride binding between the two striata [54–57]. Therefore, there is no evidence for STN stimulation inducing dopamine release in humans.

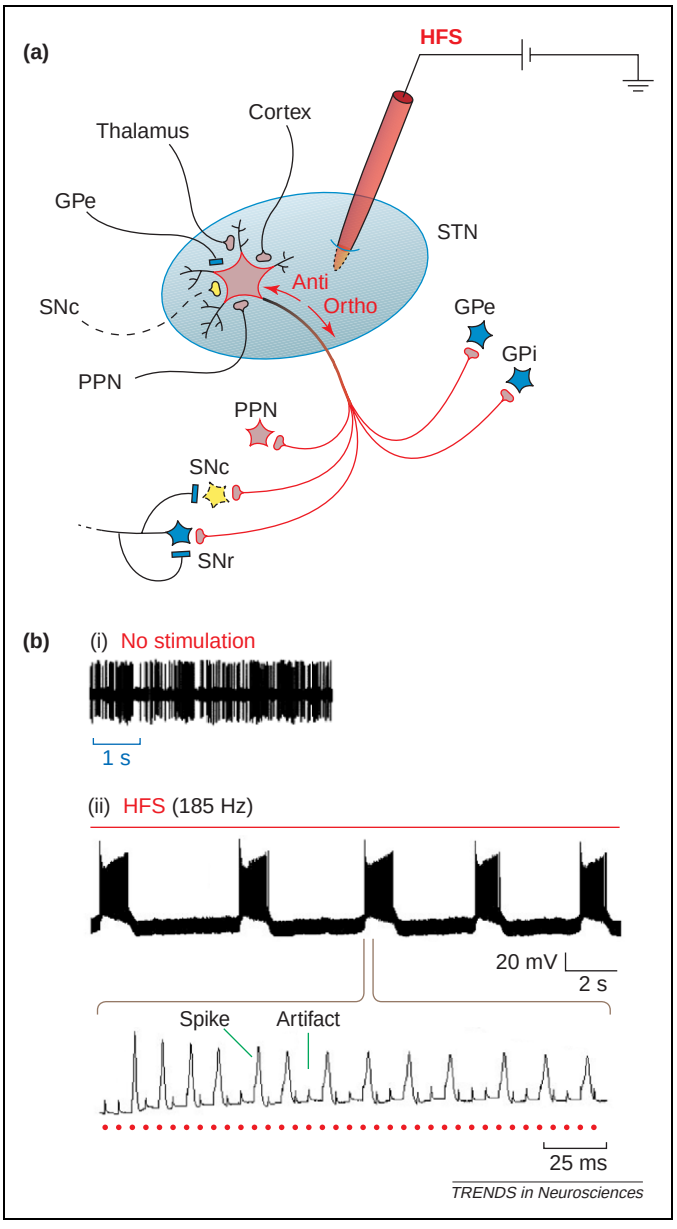

Figure 4. The 'more' hypothesis. **(a)** High-frequency stimulation (HFS) of the subthalamic nucleus (STN) directly activates STN efferent axons or somata. A new pattern that replaces the pathological one propagates orthodromically (ortho) to the various target structures of the STN: the external and internal segments of the pallidum (GPe and GPi), the substantia nigra pars reticulata (SNr) and pars compacta (SNc) and the pedunculopontine nucleus (PPN). Recurrent collaterals of SNr neurons terminate on dopaminergic neurons in the SNc and on GABAergic neurons in the SNr. Notice that in the case of parkinsonism, dopaminergic cells and terminals have degenerated (broken lines). Pink indicates glutamatergic or cholinergic terminals, blue indicates GABAergic terminals, and yellow indicates dopaminergic terminals. When axons are first activated, the HFS-driven pattern also propagates antidromically (anti) to STN cell bodies. **(b)** The disrupted activity of STN neurons recorded in a 6-hydroxydopamine-treated rat *in vivo* (i) [70] would be entirely replaced during HFS by a stable HFS-driven pattern consisting of bursts of evoked spikes (ii). The expanded trace shows the absence of spontaneous spikes in between stimuli.

Shortcomings of the 'more' hypothesis

These results suggest that HFS (i) prevents cells from discharging their network-driven (spontaneous) activity and (ii) replaces it by an activity entirely driven by HFS. It can be argued that in STN slices, HFS has a different effect from *in vivo*, owing to absence of the basal ganglia circuitry. Studies in target nuclei contradict this hypothesis because excitatory responses that have latencies compatible with the speed of conduction along the subthalamo–pallidal and subthalamo–nigral pathways are recorded. In animal models, STN-HFS increases striatal dopamine release, but this cannot provide information on the effect of HFS on STN neurons because of the complexity of intra-nigral connections and the autoregulation of dopaminergic neurons [58,59]. The presence of HFS-evoked spikes during HFS could seem to contradict the observation of an inhibitory period just after the end of HFS. Indeed, driving of STN neurons by HFS stops once HFS is over, but the concomitant inhibitory effect on spontaneous activity persists for some seconds or minutes after the end of HFS.

The hypothesis of a prokinetic rhythm

The question of how stimulation deep in the basal ganglia restores motor function in patients suffering from Parkinson's disease is important because these subcortical nuclei have a pivotal role in encoding sensorial and cognitive information (i.e. cortical outflow) to produce the automatic execution of learned movements [60]. The different hypotheses on the mechanisms of action of HFS have very different consequences. The inhibitory hypothesis (silencing effect) implies that HFS is a functional ablation that 'suppresses' STN activity from the network (i.e. 'less'). The idea is that no activity at the level of the STN outflow is preferable to a noisy and disruptive output. The reverse hypothesis, an excitatory effect, is that new evoked single spikes introduced into the STN discharge superimpose on the network-driven activity. LFS has exactly this effect, and is known to be non-therapeutic [3,18]. The 'more' hypothesis that we propose is totally different from a simple excitation and appears with stimulation at high frequency. Following our initial report [21], we propose that HFS excites the stimulated structure, evokes a regular pattern time-locked to the stimulation, which overrides the pathological STN activity. As a consequence, HFS removes the STN deleterious pattern and also introduces a new and regular pattern (Figure 3a), which exerts a positive action on the dopamine-deficient network (i.e. 'more'). The need for a high frequency ($\geq$80 Hz) to obtain the dual effect of HFS can be explained by the fact that stimuli must be close enough to one another to allow summation of inward Ca^{2+} currents and to trigger Ca^{2+} bursts. Only bursts of 60–80 Hz spikes seem able to overcome the spontaneous deleterious activity. As a result, we propose that the pathological disrupted activity recorded in the STN *in vivo* (Figure 4b,i) is totally replaced by an intermittent and stable activity in the 60–80 Hz range (Figure 4b,ii).

HFS achieves its dual effect by directly activating afferent axons, somas and efferent axons in the STN. Activation of afferent axons inside the STN and spontaneous afferent synaptic activity do not have a role in HFS, because synaptic transmission does not follow long-term HFS and/or because its postsynaptic effects are overcome by direct activation of STN neurons. By contrast, activation of somas and efferent axons gives rise to the HFS-driven activity, which is propagated othodromically to STN terminals (Figure 4a). HFS is likely to exert a widespread effect inside (Figures 1, 4a) and outside the

basal ganglia network, as recently modeled [61], because all of the basal ganglia nuclei, not just the STN, dysfunction in the parkinsonian state.

The 'more' hypothesis is in agreement with the concept of the prokinetic high-frequency rhythm, first proposed by Brown and Marsden [62]. In untreated patients and primate models of parkinsonism, local field potentials that represent synchronous activity in many neurons are dominated in the STN and GPi by low-frequency oscillations in the 11–30 Hz band [63–65]. Treatment with L-dopa encourages synchronized oscillations at frequencies >70 Hz [66] and concomitantly improves parkinsonism. The reduction of a pathological 11–30 Hz rhythm and the introduction of a high-frequency rhythm [67,68] could provide a common mechanism for therapeutic effects of L-dopa and deep brain stimulation [69].

Concluding remarks

In keeping with the present understanding of how oscillating networks operate, we propose that the improvement generated by HFS is due to parallel non-exclusive actions: silencing of ongoing activity and generation of an activity pattern in the gamma range. In theory, there is an important advantage in silencing spontaneous activity and imposing a pattern: the signal-to-noise ratio and the functional significance of the new signal is enhanced. The next step will be to identify how this new HFS-driven activity is propagated inside the basal ganglia. The fact that the most beneficial actions are produced in the high gamma range is interesting because it raises the issue of links between the integrative actions of this pattern and motor coordination.

Acknowledgements

We wish to thank C. Beurrier and Y. Ben-Ari for critical reading of the manuscript.

References

1 Limousin, P. *et al*. (1995) Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 345, 91–95
2 Limousin, P. *et al*. (1998) Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N. Engl. J. Med.* 339, 1105–1111
3 Moro, E. *et al*. (2002) The impact on Parkinson's disease of electrical parameter settings in STN stimulation. *Neurology* 59, 706–713
4 Bergman, H. *et al*. (1994) The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *J. Neurophysiol.* 72, 507–520
5 Hassani, O.K. *et al*. (1996) Increased subthalamic neuronal activity after nigral dopaminergic lesion independent of disinhibition via the globus pallidus. *Neuroscience* 72, 105–115
6 Hutchison, W.D. *et al*. (1998) Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. *Ann. Neurol.* 44, 622–628
7 Wichmann, T. *et al*. (1999) Comparison of MPTP-induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia nigra pars reticulata in primates. *Exp. Brain Res.* 125, 397–409
8 Magnin, M. *et al*. (2000) Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. *Neuroscience* 96, 549–564
9 Bergman, H. *et al*. (1990) Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* 249, 1436–1438
10 Aziz, T.Z. *et al*. (1991) Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. *Mov. Disord.* 6, 288–292
11 Benazzouz, A. *et al*. (1993) Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. *Eur. J. Neurosci.* 5, 382–389
12 Lang, A.E. (2000) Surgery for Parkinson disease: A critical evaluation of the state of the art. *Arch. Neurol.* 57, 1118–1125
13 Levy, R. *et al*. (2001) Lidocaine and muscimol microinjections in subthalamic nucleus reverse parkinsonian symptoms. *Brain* 124, 2105–2118
14 Ranck, J.B. (1975) Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res.* 98, 417–440
15 Bevan, M.D. and Wilson, C.J. (1999) Mechanisms underlying spontaneous oscillation and rhythmic firing in rat subthalamic neurons. *J. Neurosci.* 19, 7617–7628
16 Rattay, F. (1999) The basic mechanism for the electrical stimulation of the nervous system. *Neuroscience* 89, 335–346
17 Grill, W. (2003) Electrically excitable nerve elements: excitation sites in peripheral and central stimulation. In *Brain Stimulation and Epilepsy* (Lüders, H., ed.), pp. 55–66, Martin Dunitz
18 Rizzone, M. *et al*. (2001) Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: effects of variation in stimulation parameters. *J. Neurol. Neurosurg. Psychiatry* 71, 215–219
19 Nowak, L.G. and Bullier, J. (1998) Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. I. Evidence from chronaxie measurements. *Exp. Brain Res.* 118, 477–488
20 Gustafsson, B. and Jankowska, E. (1976) Direct and indirect activation of nerve cells by electrical pulses applied extracellularly. *J. Physiol.* 258, 33–61
21 Garcia, L. *et al*. (2003) Dual effect of high-frequency stimulation on subthalamic neuron activity. *J. Neurosci.* 23, 8743–8751
22 Thompson, S.M. and Gahwiler, B.H. (1989) Activity-dependent disinhibition. I. Repetitive stimulation reduces IPSP driving force and conductance in the hippocampus *in vitro*. *J. Neurophysiol.* 61, 501–511
23 Lozano, A.M. *et al*. (2002) Deep brain stimulation for Parkinson's disease: disrupting the disruption. *Lancet Neurol.* 1, 225–231
24 Filali, M. *et al*. (2004) Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. *Exp. Brain Res.* 156, 274–281
25 Welter, M.L. *et al*. (2004) Effects of high-frequency stimulation on subthalamic neuronal activity in parkinsonian patients. *Arch. Neurol.* 61, 89–96
26 Burbaud, P. *et al*. (1994) Effect of subthalamic high frequency stimulation on substantia nigra pars reticulata and globus pallidus neurons in normal rats. *J. Physiol. (Paris)* 88, 359–361
27 Tai, C.H. *et al*. (2003) Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridles neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. *FASEB J.* 17, 1820–1830
28 Beurrier, C. *et al*. (2001) High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. *J. Neurophysiol.* 85, 1351–1356
29 Lee, K.H. *et al*. (2004) Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. *J. Neurosurg.* 101, 511–517
30 Beurrier, C. *et al*. (2000) Slowly inactivating sodium current (INap) underlies single-spike activity in rat subthalamic neurons. *J. Neurophysiol.* 83, 1951–1957
31 Magarinos-Ascone, C. *et al*. (2002) High-frequency stimulation of the subthalamic nucleus silences subthalamic neurons: a possible cellular mechanism in Parkinson's disease. *Neuroscience* 115, 1109–1117
32 Hirsch, E.C. *et al*. (2000) Metabolic effects of nigrostriatal denervation in basal ganglia. *Trends Neurosci.* 23, S78–S85
33 Salin, P. *et al*. (2002) High-frequency stimulation of the subthalamic nucleus selectively reverses dopamine denervation-induced cellular defects in the output structures of the basal ganglia in the rat. *J. Neurosci.* 22, 5137–5148
34 Lee, K.H. *et al*. (2003) Effect of high-frequency stimulation of the subthalamic nucleus on subthalamic neurons: an intracellular study. *Stereotact. Funct. Neurosurg.* 80, 32–36
35 Beurrier, C. *et al*. (1999) Subthalamic nucleus neurons switch from single-spike activity to burst-firing mode. *J. Neurosci.* 19, 599–609
36 Rinvik, E. and Ottersen, O.P. (1993) Terminals of subthalamonigral

fibres are enriched with glutamate-like immunoreactivity: an electron microscopic, immunogold analysis in the cat. *J. Chem. Neuroanat.* 6, 19–30
37 Hammond, C. *et al*. (1978) Electrophysiological demonstration of an excitatory subthalamonigral pathway in the rat. *Brain Res.* 151, 235–244
38 Nakanishi, H. *et al*. (1991) Intracellular study of rat entopeduncular nucleus neurons in an *in vitro* slice preparation: response to subthalamic stimulation. *Brain Res.* 549, 285–291
39 Féger, J. *et al*. (1997) The subthalamic nucleus and its connections. New electrophysiological and pharmacological data. *Adv. Neurol.* 74, 31–43
40 Maurice, N. *et al*. (2003) Spontaneous and evoked activity of substantia nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. *J. Neurosci.* 23, 9929–9936
41 Hashimoto, T. *et al*. (2003) Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J. Neurosci.* 23, 1916–1923
42 Nambu, A. *et al*. (2000) Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. *J. Neurophysiol.* 84, 289–300
43 Ceballos-Baumann, A.O. *et al*. (1999) A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease: enhanced movement-related activity of motor-association cortex and decreased motor cortex resting activity. *Arch. Neurol.* 56, 997–1003
44 Hershey, T. *et al*. (2003) Cortical and subcortical blood flow effects of subthalamic nucleus stimulation in PD. *Neurology* 61, 816–821
45 Zhao, Y.B. *et al*. (2004) Effects of bilateral subthalamic nucleus stimulation on resting-state cerebral glucose metabolism in advanced Parkinson's disease. *Chin Med. J. (Engl.)* 117, 1304–1308
46 Windels, F. *et al*. (2000) Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. *Eur. J. Neurosci.* 12, 4141–4146
47 Windels, F. *et al*. (2003) Influence of the frequency parameter on extracellular glutamate and γ-aminobutyric acid in substantia nigra and globus pallidus during electrical stimulation of subthalamic nucleus in rats. *J. Neurosci. Res.* 72, 259–267
48 Rosales, M.G. *et al*. (1997) Reciprocal interaction between glutamate and dopamine in the pars reticulata of the rat substantia nigra: a microdialysis study. *Neuroscience* 80, 803–810
49 Groenewegen, H.J. and Berendse, H.W. (1990) Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat. *J. Comp. Neurol.* 294, 607–622
50 Bruet, N. *et al*. (2001) High frequency stimulation of the subthalamic nucleus increases the extracellular contents of striatal dopamine in normal and partially dopaminergic denervated rats. *J. Neuropathol. Exp. Neurol.* 60, 15–24
51 Meissner, W. *et al*. (2003) High-frequency stimulation of the subthalamic nucleus enhances striatal dopamine release and metabolism in rats. *J. Neurochem.* 85, 601–609
52 Meissner, W. *et al*. (2004) High frequency stimulation of the entopeduncular nucleus has no effect on striatal dopaminergic transmission. *Neurochem. Int.* 44, 281–286
53 Laruelle, M. (2000) Imaging synaptic neurotransmission with *in vivo* binding competition techniques: a critical review. *J. Cereb. Blood Flow Metab.* 20, 423–451
54 Abosch, A. *et al*. (2003) Stimulation of the subthalamic nucleus in Parkinson's disease does not produce striatal dopamine release. *Neurosurgery* 53, 1095–1102
55 Hilker, R. *et al*. (2003) Deep brain stimulation of the subthalamic nucleus does not increase the striatal dopamine concentration in parkinsonian humans. *Mov. Disord.* 18, 41–48
56 Strafella, A.P. *et al*. (2003) Subthalamic deep brain stimulation does not induce striatal dopamine release in Parkinson's disease. *NeuroReport* 14, 1287–1289
57 Thobois, S. *et al*. (2003) Chronic subthalamic nucleus stimulation and striatal D2 dopamine receptors in Parkinson's disease – A [^{11}C]-raclopride PET study. *J. Neurol.* 250, 1219–1223
58 Smith, I.D. and Grace, A.A. (1992) Role of the subthalamic nucleus in the regulation of nigral dopamine neuron activity. *Synapse* 12, 287–303
59 Bunney, B.S. *et al*. (1973) Comparison of effects of L-dopa, amphetamine and apomorphine on firing rate of rat dopaminergic neurones. *Nat. New Biol.* 245, 123–125
60 Marsden, C.D. (1982) The mysterious motor function of the basal ganglia: the Robert Wartenberg Lecture. *Neurology* 32, 514–539
61 Rubin, J.E. and Terman, D. (2004) High frequency stimulation of the subthalamic nucleus eliminates pathological thalamic rhythmicity in a computational model. *J. Comput. Neurosci.* 16, 211–235
62 Brown, P. and Marsden, C.D. (1998) What do the basal ganglia do? *Lancet* 351, 1801–1804
63 Nini, A. *et al*. (1995) Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. *J. Neurophysiol.* 74, 1800–1805
64 Brown, P. *et al*. (2001) Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J. Neurosci.* 21, 1033–1038
65 Levy, R. *et al*. (2002) Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. *J. Neurosci.* 22, 2855–2861
66 Williams, D. *et al*. (2002) Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. *Brain* 125, 1558–1569
67 Montgomery, E.B. and Baker, K.B., Jr. (2000) Mechanisms of deep brain stimulation and future technical developments. *Neurol. Res.* 22, 259–266
68 McIntyre, C. and Grill, W.M. (2002) Extracellular stimulation of central neurons: influence of stimulus waveform and frequency on neuronal output. *J. Neurophysiol.* 88, 1592–1604
69 Brown, P. *et al*. (2004) Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. *Exp. Neurol.* 188, 480–490
70 Hassani, O.K. and Féger, J. (1999) Effects of intrasubthalamic injection of dopamine receptor agonists on subthalamic neurons in normal and 6-hydroxydopamine-lesioned rats: an electrophysiological and c-fos study. *Neuroscience* 92, 533–543