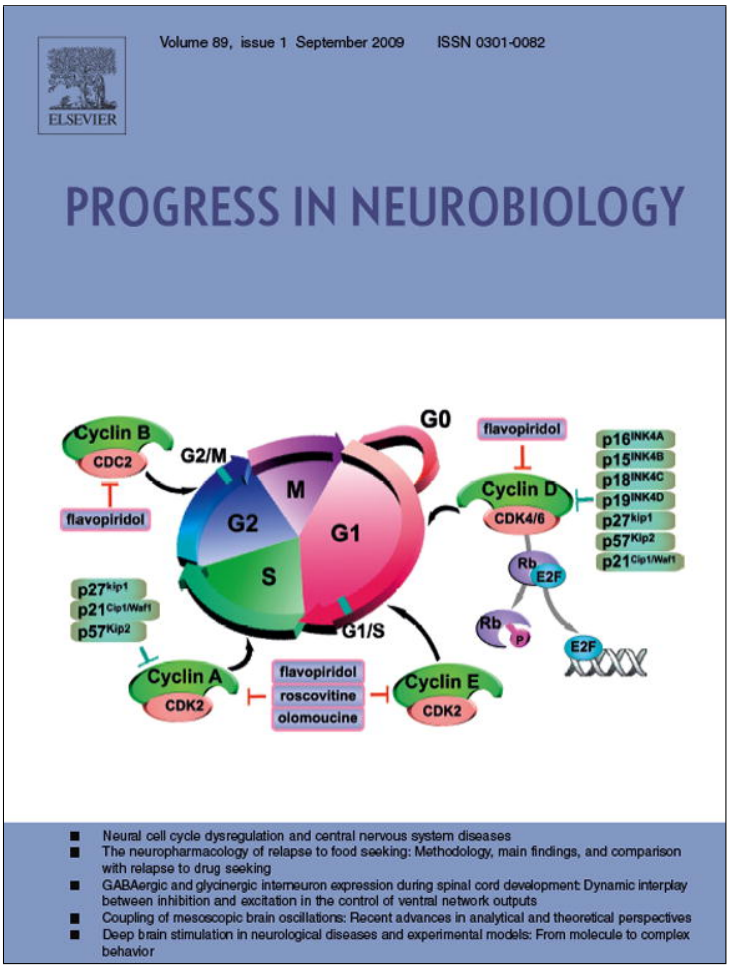

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Deep brain stimulation in neurological diseases and experimental models: From molecule to complex behavior

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ABSTRACT

Deep brain stimulation (DBS) has proven to be capable of providing significant benefits for several neuropathologies. It is highly effective in reducing the motor symptoms of Parkinson's disease, essential tremor, and dystonia, and in alleviating chronic pain. Recently, also Tourette syndrome, obsessive–compulsive disorder and treatment-resistant depression have been treated by DBS with encouraging results. However, despite these clinical achievements, the precise action mechanisms of DBS still need to be fully characterized. For this reason, several animal models of DBS have been developed, bringing new insights on the effects of this treatment at molecular and cellular level, and providing new evidence on its physiological and behavioral consequences. In parallel, physiological and imaging studies in patients have contributed to better understanding DBS impact on the function of brain circuits. Here we review the clinical data and experimental work *in vitro*, *ex vivo* and *in vivo* (mostly arisen from studies on DBS of the subthalamic nucleus) in the treatment of PD, which led to the actual knowledge of DBS mechanisms, from molecular to complex behavioral levels.

Contents

Abbreviations: AP, action potential; BG, basal ganglia; CM/Pf, centre median–parafascicular complex of the thalamus; COI, cytochrome oxydase complex 1; DA, dopamine; DBS, deep brain stimulation; EEG, electroencephalographic, electroencephalogram or electroencephalography; EP, entopeduncular nucleus; GPe/i, external/internal segment of the globus pallidus; HD, Huntington's disease; HFS, high-frequency stimulation; LFS, low-frequency stimulation; NAc, nucleus accumbens; OCD, obsessive–compulsive disorder; PD, Parkinson's disease; PET, positron emission tomography; PPN, pedunculopontine nucleus; RMP, resting membrane potential; SNc/r, substantia nigra pars compacta/reticulata; STN, subthalamic nucleus; TRD, treatment-resistant depression; UPDRS, Unified Parkinson's Disease Rating Scale; VIM, ventral intermediate nucleus of the thalamus; VP, ventral pallidum; VTA, ventral tegmental area; ZI, zona incerta.

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1. Introduction

Deep brain stimulation (DBS) is now widely utilized as a functional surgical strategy for the treatment of a variety of neurological and psychiatric disorders. DBS at high frequency, also called high-frequency stimulation (HFS), has been shown to mimic the effects of lesioning the targeted structure and has thus widely replaced the ablative procedures. For example, the tremor characterizing Parkinson's disease (PD) as well as essential tremor is reduced by delivering DBS at high frequency to the ventral intermediate nucleus of the thalamus (VIM). A great improvement of the cardinal PD motor symptoms is achieved by HFS of the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi), two structures of the basal ganglia (BG). DBS is also applied for the treatment of pain, dystonia, Tourette syndrome, refractory epilepsy, depression, obsessive–compulsive disorder (OCD), obesity and minimal conscious states.

Electrical stimulation assisted by stereotaxy was developed in the late 1940s in order to help identify and map deep brain structures (Spiegel et al., 1947). Since the 1950s, DBS has been utilized for intrasurgical localization prior to therapeutic lesion of several brain structures, in particular for pallidotomy and thalamotomy (Spiegel and Wycis, 1952), and anecdotally reported as a therapy for untreatable pain syndromes (Bittar et al., 2005; Tasker and Vilela, 1995). Although nowadays DBS is mainly used to alleviate neurological motor disorders, it was only in the 1960s that DBS of the ventrolateral thalamus was first reported to alleviate tremor (Hassler et al., 1960; Ohye et al., 1964). However, during this decade DBS was still utilized for targeting a brain region prior to its lesion: in some cases, DBS was delivered with chronically implanted electrodes over a period that could reach several days, in order to best define the target to be lesioned. In the 1970–1980s, the therapeutic use of chronic DBS of the cerebellum emerged for treating movement disorders or epilepsy (Brice and McLellan, 1980; Cooper, 1973; Cooper et al., 1973, 1976), and thalamic DBS was used for alleviating pain (Hosobuchi et al., 1973). In particular, Benabid et al. (1987) reported that stimulating the VIM at high frequency could

ameliorate PD tremor during the targeting procedure for surgical lesioning of this structure. Such observation led to the application of chronic VIM HFS for the treatment of PD, essential tremor and extra-pyramidal dyskinesias, which was the first example of DBS at high frequency delivered by chronically implanted electrodes connected to a pacemaker-like portable stimulator (Benabid et al., 1989, 1991). Since then, this surgical technique, applied to several brain structures, has become widespread for the treatment of a variety of brain disorders. However, despite its undoubtedly therapeutic efficacy, there are still several controversies about its action mechanisms and the long-term impact on neuronal circuits. A considerable amount of data has thus been produced experimentally in order to address this issue. Here we will provide a wide review of the data obtained from experimental models of DBS at molecular, cellular, physiological and behavioral levels, which contributed to a better understanding of the mechanisms and the consequences of this treatment. We will also refer to the accumulating functional investigations performed in patients with DBS neurosurgery. A comprehensive list of stimulation parameters, electrode features, experimental models, and DBS targets described in the scientific reports reviewed here is provided in Table 1.

2. Neurophysiological mechanisms of deep brain stimulation

2.1. Basic principles of DBS

At the beginning of the 20th century, Georges Weiss was the first to investigate quantitatively the basic principles of electrostimulation (Weiss, 1901). In his pioneering 1901 paper "*Sur la possibilité de rendre comparables entre eux les appareils servant à l'excitation électrique*" (On the possibility of rendering mutually comparable the devices used for electrical excitation), Weiss tried to find an answer to the following questions, some of which are still open today: "Coming to nerves and muscles; if they are excited electrically, on what is this excitation based? On intensity, on potential, on electrical energy? Or perhaps on what other electrical quantity?" To address these issues, he conceived a clever electro-mechanic device for measuring the relationship between stimulus amplitude and duration of monophasic pulses in the 200–3000 μs range. Galvanic stimulation systems with longer stimuli duration (in the second range) were not included in his analysis, because long pulses produce electrolytic effects (accommodation). Weiss' results on electrostimulation are summarized in three theorems:

1. The threshold time-dependent quantity Q [which is the voltage–time-product $V(t)\,dt$] is a linear function of the pulse duration t:
$$Q(t) = a + bt \qquad \text{(a)}$$
where the coefficients a and b depend upon experimental conditions. Weiss called this formula "the fundamental law of electrostimulation".
2. There is always a minimum of derived energy that depends on pulse duration. It was another French scientist, Lapique (1909), who realized that this "minimum energy" is a/b, later called *chronaxie*, where b is the *rheobase* (rheobase is the minimal electric current of infinite duration resulting in an action potential; chronaxie is the minimum time over which an electric current double the strength of the rheobase needs to be applied in order to stimulate a nerve cell).
3. The shape of the electric pulse does not play a role in electrostimulation.

Lapique further developed Weiss' concepts and the resulting equation, derived by dividing both sides of (a) by t, is

Table 1
List of the electrode features, stimulation parameters, experimental model, and brain target for DBS, ordered by reference (leftmost column).

References	Intensity[a] (μA)	Freq. (Hz)	PW (μs)	Waveform	Electrode type	Electrode size	Duration	Animal	Condition	Brain target	Side	Topic
Anderson et al. (2004)	0.86–6.4	125	60	Mono–biphasic	Bipolar tungsten	0.1 mm diameter, 0.75 mm pole separation	10 s	Rat	Slice	Ventrolat. and ventropost. thal.	Unilateral	Mechanisms
Anderson et al. (2006)	250–5000	125	60–80	ND	Concentric bipolar stainless steel (NEX-100)	200 μm tip diameter	1–30 s	Rat	Slice	Ventral thalamus	Unilateral	Mechanisms
Baunez et al. (2007)	50	130	60	Monophasic	Bipolar platinum–iridium (2 wires, custom-made)	76 μm tip diameter (insulated 110 μm; tip separation 100 μm)	30 min daily	Rat	Awake	STN	Bilateral	PD
Baup et al. (2008)	0–3 V	130	60	Biphasic	Four platinum–iridium contacts (unipolar stimulation)	1 mm of contact length spaced by 0.5 mm	ND	Monkey	Awake	STN	Unilateral	OCD
Benazzouz et al. (1995)	100–1000	1–1000	60	Monophasic	Concentric bipolar	200 μm tip diameter	5 s	Rat	Anesthetized	STN	Unilateral	Mechanisms
Benazzouz et al. (2000b)	10–1000	130	500	Monophasic	Concentric bipolar	200 μm tip diameter	5 s	Rat	Anesthetized	STN	Unilateral	Mechanisms
Bergmann et al. (2004)	50–200	130	100	Biphasic	Bipolar concentric steel (SNE-100)	100 μm tip diameter	1 min	Rat	Awake	STN	Unilateral	Mechanisms
Beurrier et al. (1997)	200–1100	60–110	100	ND	Bipolar concentric	ND	1–3 min	Monkey	Awake	STN	Unilateral	Hemiballism

Table 1 (*Continued*)

References	Intensity[a] (μA)	Freq. (Hz)	PW (μs)	Waveform	Electrode type	Electrode size	Duration	Animal	Condition	Brain target	Side	Topic
Beurrier et al. (2001)	5–8 V	100–250	100	Monophasic	concentric Bipolar stainless steel (NEX-100)	200 μm tip diameter	1 min	Rat	Slide	STN	Unilateral	Mechanisms
Boulet et al. (2006)	0–350	10–200	20–100	Monophasic	Monopolar platinum–iridium	76 μm tip diameter (insulated 110 μm; tip separation 100 μm)	1 h	Rat	Awake	STN	Unilateral	PD
Cuellar-Herrera et al. (2006)	100–400	130	60	Biphasic	Two twisted stainless steel wires	Cross-section of the two tips as active zone (tip separation 0.5 mm)	1 h	Rat	Awake	STN	Bilateral	Epilepsy
Darbaky et al. (2003)	50–300	130	60	Monophasic	Bipolar twisted stainless steel and platinium	0.1 mm tip distance	90 min daily	Rat	Awake	STN	Unilateral	PD
Dorval et al. (2008)	2.4–4 V	136	90–140	Biphasic	Four platinum–iridium contacts	0.76 mm contact diameter, 0.5 mm height, 0.5 mm contact separation	ND	Monkey	Awake	STN	Unilateral	PD
Fang et al. (2006)	200	130	60	ND	Bipolar double-cored polyurethane-insulated stainless steel	100 μm tip diameter (shaft 400 μm; tip separation 100 μm)	1 h daily	Rat	Awake	STN	Unilateral	PD
Feddersen et al. (2007)	<300	50–500	10–200	Mono/biphasic	Mono- and bipolar stainless steel	175 μm twisted wire	5 s	Rat	Awake	SNr	Mono/bilat	Epilepsy
Florio et al. (2007)	100–1000	130	60	Monophasic	Bipolar concentric	ND	1–5 s	Rat	Anesthetized	PPN	Unilateral	Mechanisms
Garcia et al. (2005a)	100–500–1500	10–130–185	60–90–400	ND	NEX-100 or RNEX-300 (monopolar configuration)	Area of active contact 0.3 and 0.2 mm^2, respectively	30 min	Rat	Slice	STN	Unilateral	Mechanisms
Gubellini et al. (2006)	80	130	80	Monophasic	Bipolar platinum–iridium (2 wires custom-made)	76 μm tip diameter (insulated 140 μm; tip separation 500 μm)	5 days	Rat	Awake	STN	Unilateral	PD
Gubellini et al. (2008)	50–150	130	60	Monophasic	Bipolar platinum–iridium (2 wires custom-made)	76 μm tip diameter (insulated 140 μm; tip separation 500 μm)	5 days	Rat	Awake	STN	Unilateral	PD
Hamani et al. (2004)	800	100	100	ND	Bipolar twisted wire	100 μm tip diameter	50 min	Rat	Awake	Anterior thalamus	Bilateral	Epilepsy
Harnack et al. (2004a)	50	130	180	Biphasic	Bipolar concentric stainless-steel (SNEX-100)	100 μm tip diameter	3 h	Hamster	Awake	EP	Bilateral	Dystonia
Hashimoto et al. (2003)	2.4–3.5 V	136–185	210	Biphasic	Four platinum–iridium contact (bipolar configuration)	0.76 mm diameter contact, 0.5 mm thickness, 0.5 mm distance	ND	Monkey	Awake	STN	Unilateral	PD
Hiller et al. (2007)	100–500	124	60	Monophasic	Bipolar platinum–iridium	75 μm cathode tip diameter	2× 30 min	Rat	Anesth/awake	Striatum	Unilateral	Mechanisms
Iremonger et al. (2006)	310	125	90	Monophasic	Bipolar tungsten or NEX-100	Tungsten electrode (0.1 mm diameter, 0.75 mm pole separation)	30 s–5 min	Rat	Slice	Subcortical white matter tracts	Unilateral	Mechanisms

Jackson et al. (2008)	200–800	100	100	Biphasic	Bipolar (Plastics ONE, # MS303 twisted stainless steel)	200 μm tip diameter	25 min	Rat	Awake	Posterior hypothal.	Unilateral	Catalepsy
Kiss et al. (2002)	500–10000	2–300	60	Monophasic	Coaxial or bipolar	0.5 mm tip distance	10–60 s	Rat	Slice	Ventral thalamus	Unilateral	Mechanisms
Klavir et al. (2009)	100	130	100	Biphasic	Bipolar concentric steel (SNE-100)	100 μm tip diameter	30 min daily	Rat	Awake	STN	Bilateral	OCD
van Kuyck et al. (2008)	100–500	2–100	50	ND	Monopolar stainless steel	200 μm tip diameter	30 min daily	Rat	Awake	NAc/bed of stria terminalis	Bilateral	Polydipsia
Lacombe et al. (2007)	200	130	60	Biphasic	Bipolar concentric stainless-steel (SNEX-100)	100 μm tip diameter	1 h	Rat	Anesthetized	STN	Unilateral	PD
Lee et al. (2006)	10–500	10–200	50–100	Monophasic	Bipolar concentric steel (SNE-100)	200 μm tip diameter	0.5 ms every 30 s	Rat	Anesthetized	STN	Unilateral	Mechanisms
Lee et al. (2007)	100–3000	10–1000	100	Monophasic	Concentric bipolar platinum–iridium	200 and 50 μm outer and inner diameter, respectively	5 s–60 min	Rat	Anesthetized	STN	Unilateral	Mechanisms
Levy et al. (2007)	200–400	100	100	ND	Monopolar (Plastics ONE)	200 μm tip diameter	30 min daily	Rat	Awake	Lateral hypothal./ prefrontal cortex	Bilateral	Addition
Li et al. (2006)	600	130	60	Monophasic	Platinum	ND	10 min	Rat	Slice	Striatum	Unilateral	Mechanisms
Li et al. (2007)	80–240	40–160	100	Biphasic	Bipolar stainless steel wires (custom-made et SNE-100)	0.081 mm and 0.25 mm tip diameter, respectively	Seconds	Rat	Anesthetized	STN	Unilateral	Mechanisms
Lim et al. (2008)	1–650	1–300	100	ND	Gold-plated needle-like and inner platinum–iridium wire	50 μm tip diameter and 250 μm shaft diameter	15 s ON–45 s OFF	Rat	Awake	Dorsolateral periaqueductal gray	Unilateral	Panic-like
Liu et al. (2008)	200–500	130	210	Monophasic	Bipolar stainless steel	Outlet metal tube (anode) 0.6 mm, inner metal core (cathode) 200 μm	3 h daily	Rat	Awake	NAc	Unilateral	Addition
Lopez-Meraz et al. (2004)	100 to 400	1	100	Biphasic	Bipolar electrode twisted stainless steel wire	ND	15 min daily	Rat	Awake	Amygdala	Unilateral	Epilepsy
Magarinos-Ascone et al. (2002)	0.1–1.0	100–130	ND	ND	Bipolar Nichrome wires	80 μm tip diameter	Few seconds	Rat	Slice	STN	Unilateral	Mechanisms
Maurice et al. (2003)	0–160	130	60	Monophasic	Concentric bipolar (SNEX-100)	100 μm tip diameter	30–60 s	Rat	Anesthetized	STN	Unilateral	Mechanisms
McCairn and Turner (2009)	200–1000	150	200	Biphasic	Bipolar platinum–iridium	50 μm tip diameter, 500 μm tip lenght	30 s every 70 s	Monkey	Awake	GPi	Unilateral	PD
McCracken and Grace (2007)	100–400	130	100	ND	Concentric bipolar stainless steel (NEX-100)	200 μm tip diameter	30 min	Rat	Anesthetized	NAc	Unilateral	OCD
Meissner et al. (2002)	300	130	60	Biphasic	Concentric bipolar stainless steel (NEX-100)	200 μm tip diameter	3 h	Rat	Awake	STN	Unilateral	PD
Meissner et al. (2003)	300	130	60	ND	Bipolar concentric stainless-steel (SNEX-100)	100 μm tip diameter	20–120 min	Rat	Anesthetized	STN	Unilateral	PD
Meissner et al. (2005)	100	130	60	Biphasic	Four platinum–iridium contacts	ND	6 min per session	Monkey	Awake	STN	Unilateral	PD

Table 1 (*Continued*)

References	Intensity[a] (μA)	Freq. (Hz)	PW (μs)	Waveform	Electrode type	Electrode size	Duration	Animal	Condition	Brain target	Side	Topic
Mirski et al. (2009)	150	100	100	ND	Bipolar steel	30 kΩ, 125 μm diameter with 250 μm separation of 50 μm exposed tips	75 min	Rat	Awake	Anterior thalamus	Bilateral	Epilepsy
Moser et al. (2003)	600	130	60	Monophasic	Monopolar configuration	ND	10 min	Rat	Slice	Striatum	Unilateral	Mechanisms
Nishida et al. (2007)	80–150	100	300	Biphasic	Polyurethane-coated stainless steel	200 μm tip diameter with 0.5 mm tip separation	10 s ON–30 min OFF	Rat	Awake	Posterior hypothal.	Unilat-bilat	Epilepsy
Oueslati et al. (2007)	80	130	80	Monophasic	Bipolar platinum–iridium (two wires custom-made)	76 μm tip diameter (insulated 140 μm; tip separation 500 μm)	5 days	Rat	Awake	STN	Unilateral	PD
Salin et al. (2002)	250	130	80	Monophasic	Twisted stainless steel Teflon-coated wires (custom-made)	Cross-section of the two tips as active zone (tip separation 0.3 mm)	2 h	Rat	Awake	STN	Unilateral	PD
Sani et al. (2007)	2 V	180–200	100	Biphasic	Bipolar (Plastics ONE)	0.25 mm tip diameter	7 days	Rat	Awake	Lateral hypothalamus	Bilateral	Obesity
Schulte et al. (2006)	300	80–130	60	ND	Bipolar concentric steel (SNE-100)	100 μm tip diameter	15–240 min	Rat	Anesthetized	STN	Bilateral	Mechanisms
Shen et al. (2003)	50–200	100	100	Monophasic	Bipolar	ND	Trains, 1 min	Rat	Slice	STN	Unilateral	Mechanisms
Shi et al. (2006a)	50–175	130	60	Biphasic	Bipolar platinum–iridium (custom-made)	50 μm tip diameter (tip separation 250–500 μm)	3–20 s	Rat	Awake	STN	Unilateral	PD
Shi et al. (2006b)	100–200	130	60	ND	ND	ND	20 s	Rat	Awake	SN	Bilateral	Epilepsy
Shin et al. (2007)	100–300	150	60	Monophasic	Concentric bipolar platinum/iridium	ND	10 s	Rat	Slide	EP	Unilateral	Mechanisms
Tai et al. (2003)	400	130	60	ND	Concentric bipolar	200 μm tip diameter	10 s–45 min	Rat	Anesthetized	STN	Unilateral	PD
Temel et al. (2005)	1–3–30–150	130	60	Biphasic	Concentric bipolar platinum–iridium	50 μm tip diameter and 350 μm shaft diameter	35 min daily	Rat	Awake	STN	Bilateral	PD
Temel et al. (2005)	3–150	10–130	60	Biphasic	Gold-plated coaxial	50 μm tip diameter, 75 μm tip length, 50 μm tip distance	2–3 min	Rat	Anesthetized	STN	Bilateral	PD
Temel et al. (2006a)	3–30–150	130	60	Biphasic	Concentric bipolar platinum–iridium	50 μm tip diameter (shaft 250 μm; tip separation 50 μm)	42 min	Rat	Awake	GP	Bilateral	HD
Toda et al. (2008)	2.5 V	10–50–130	90	ND	Bipolar concentric stainless-steel (SNEX-100)	100 μm tip diameter	1 h	Rat	Anesthetized	Anterior thalamus	Bilateral	Mechanisms
Vassoler et al. (2008)	150	160	60	Biphasic	Bipolar stainless steel (Plastic ONE)	0.25 mm tip diameter	2 h	Rat	Awake	NAc	Bilateral	Addiction
Vercueil et al. (1998)	0–300	130	60	Monophasic	Concentric bipolar	200 μm tip diameter	5 s	Rat	Awake	STN	Bilateral	Epilepsy
Wang et al. (2008)	100	3	100	Monophasic	Twisted stainless steel Teflon-coated wires (A.M. Systems, USA)	200 μm tip diameter, 0.5–0.8 mm tip separation	15 min daily	Rat	Awake	Fastigial nucleus	Unilateral	Epilepsy
Windels et al. (2005)	500	130	60	ND	Concentric bipolar stainless steel (NEX-100)	200 μm tip diameter	60 min	Rat	Anesthetized	STN	Unilateral	PD
Winter et al. (2008a)	300	130	60	ND	Bipolar concentric stainless-steel (SNEX-100)	100 μm tip diameter	20 min	Rat	Anesthetized	STN	Unilateral	PD

Wu et al. (2007)	1.8 V	50–300	100	ND	Bipolar concentric stainless-steel (SNEX-100)	100 μm tip diameter	30–90 s	Rat	Anesthetized	Ventral medullary reticular formation	Unilateral	Arousal
Wu et al. (2008)	100–200	1–50–100	100	Monophasic	Bipolar twisted stainless steel Teflon-coated wires	tip distance 0.5–1.0 mm	15 min daily	Rat	Awake	Amygdala	Unilateral	Epilepsy
Wyckhuys et al. (2007)	100	130	60	Biphasic	Bipolar (custom-made)	ND	7 days	Rat	Awake	Hippocampus	Unilateral	Epilepsy
Ziai et al. (2005)	150	100	100	ND	Bipolar steel	125 μm tip diameter (tip separation 250 μm)	4 h	Rat	Anesthetized	Anterior thalamus	Unilateral	Epilepsy

PW = pulse width.
[a] Intensity is expressed in μA, except when stated differently.

$Q(t)/t = a/t + b = b[1 + (a/b)/t]$; this can be expressed as:

$$\frac{Q(t)}{t} = U_{rh}\left(1 + \frac{t_{ch}}{t}\right) \quad \text{(b)}$$

where U_{rh} is the rheobase and t_{ch} is the chronaxie. Correct values for rheobase and chronaxie are only achievable if mean voltages, and not peak voltages, are used to construct the strength–duration curve or the Weiss straight line; thus, we can calculate that:

$$\frac{Q(t)}{t} = \left(\frac{1}{t}\right)\int_0^t U(\tau)\,d\tau = U_{th} \quad \text{(c)}$$

where U_{th} is the time-averaged threshold voltage during the pulse duration t. In conclusion, Weiss–Lapique relationship between stimulus amplitude and duration of pulse (b) can be simplified as:

$$U_{th} = U_{rh}\left(1 + \frac{t_{ch}}{t}\right) \quad \text{(d)}$$

or, in terms of current (which is the most operatively used parameter), as:

$$I_{th} = I_{rh}\left(1 + \frac{t_{ch}}{t}\right) \quad \text{(d′)}$$

where I_{th} is the threshold current and I_{rh} is the rheobase current (Irnich, 2002).

Although the relationship between the amplitude and the width of the stimulating pulse expressed by Eqs. (d) and (d′) looks fairly simple, electrical stimulation of the brain is a far more complex matter. This is mainly due to the anisotropic nature of the tissue surrounding the electrodes, and the heterogeneous electrophysiological properties of the stimulated elements at cellular and structure level. First of all, different neuronal elements have different chronaxies: for example, large myelinated fibers have chronaxies ranging around 30–200 μs, while for cell bodies and dendrites this value is around 1–10 ms (Ranck, 1975). Given these values, it seems likely that most of the effects of DBS primarily result from the activation of axons rather than of dendrites or cell bodies. Accordingly, clinical studies aimed at measuring chronaxies in human VIM and GPi found that in these structures, where chronaxie is around 60–75 μs, DBS effects are likely mediated through the activation of afferent and efferent axons (Holsheimer et al., 2000a, 2000b). In line with these findings, cortical stimulation also results in the activation of efferent axons, even when a depolarization block is induced in cell bodies and initial axon segment (Nowak and Bullier, 1998a, 1998b). An interesting working hypothesis, confirmed by experimental and model data, is that the activity in the axon and the cell body of stimulated neurons is decoupled. In general, cathodic stimuli trigger membrane depolarization in regions proximal to the electrode, while hyperpolarization is generated around the region of depolarization. This can result in cell body hyperpolarization coupled with action potential initiation in the axon (McIntyre and Grill, 1999; Nowak and Bullier, 1998a, 1998b). The overall effect will be that neuronal firing of the target structure is silenced, but its synaptic output increased (McIntyre et al., 2004a, 2004b). Moreover, it must also be considered that the threshold of axon terminals projecting to the region around the electrode is lower than the threshold for direct activation of local cells. The activation of these "trans-synaptic" inputs can thus participate in the decoupling of cell body and axon activity (McIntyre et al., 2004a). A recent study, using innovative genetic and optic tools to drive or inhibit distinct elements of the STN microcircuitry in a rodent PD model, provided further evidence that the therapeutic effects of STN HFS are due to direct selective stimulation of afferent axons projecting to this region (Gradinaru et al., 2009).

Another important factor that can affect the responsiveness to DBS is the relationship between the orientation of the axons and

the current flow (or the voltage gradient). It is known that, when they are parallel, the efficacy of DBS is maximal (Ranck, 1975). Thus, the electrode configuration and its placement in the stimulated structure are critical for determining the results of DBS. Moreover, it should be considered that different brain structures have different conductivities, and that this parameter itself can vary as a consequence of the neurophysiological changes occurring in different states of the neurological disease for which DBS is applied (see also Section 2.2). It should also be taken into account that the values of both chronaxie and rheobase rise when increasing the distance between the electrode and the targeted axons (Holsheimer et al., 2000a, 2000b; West and Wolstencroft, 1983). While this factor could limit the diffusion of the stimuli to the targeted brain area, the above-mentioned preferential activation of axons implies that local DBS can activate other interconnected brain structures. In this context, a very recent computational model of GPi DBS (Johnson and McIntyre, 2008) further suggests that such treatment may have a broader effect than on GPi itself: DBS can activate STN axons projecting to the external segment of the globus pallidus (GPe) and passing through the GPi, as well as striatonigral fibers, dopaminergic fibers from the substantia nigra pars compacta (SNc) and other bundles of axons passing or collateralizing into the GPi. Thus, the effects of DBS might depend on the relative proportion of GPi and/or GPe efferents directly affected by the stimulation.

2.2. Technical issues about DBS

2.2.1. Tissue reactivity to electrode implantation and DBS timing

To date, most of the studies in experimental models of DBS (see Table 1) rely on acute stimulation (seconds to a couple of hours), and they often draw conclusions on chronic stimulation applied in patients. We will see in this review that critical mechanisms of acute DBS strongly differ from those of chronic DBS. Knowing the state of the electrode–tissue interface in DBS is an important issue in evaluating the chronic viability of such applications. Several factors, including mechanical movement, electrode degradation (by electrolysis), and changes in tissue morphology/chemistry, can modify the electrical impedance of a given electrode–tissue interface (Merrill et al., 2005). It is well established that the components of the electrode–brain interface change during the 6–8 weeks post-implantation in humans. The perielectrode space is filled first with extracellular fluid at few days after post-implantation (Thoma et al., 1987; Xie et al., 2006), then by giant cell growth and/or microglia formation (Griffith and Humphrey, 2006; Moss et al., 2004). The changes of the biophysical properties of this interface affect the electric field (shape and size) crossing this area during stimulation. Thus, in order to minimize this problem in experimental animals, electrodes should be implanted at least some days before DBS application. Recent computational works have shown that extracellular potential in the brain volume surrounding the electrode is stronger at early stages than at chronic stages, due to the higher conductivity of extracellular fluid compared to encapsulation tissue (Yousif et al., 2007, 2008a). These studies have also shown that the different composition of the perielectrode space in the acute vs. chronic time stages post-implantation induces a dramatic waveform distortion. In the acute stage, the tissue capacitance dominates, inducing a low-pass filter behavior whereas, at chronic stages, the capacitance of the encapsulation tissue takes over, attenuating the waveform shape (Yousif et al., 2008b).

A recent study in humans shows that short (90 min) and long (3 months) STN DBS periods are equally efficient in improving motor deficits of PD, suggesting that acute DBS clinical trials and research studies are relevant to evaluate the impact of DBS (Sturman et al., 2008). The authors further suggest that, in contrast to GPi DBS for dystonia, which is characterized by delayed and progressive appearance of the beneficial effects, the mechanism of STN DBS in PD may involve an action on the pathological oscillatory BG activity rather than on synaptic reorganization. However, it is to note that, as mentioned by the authors in this study, comparative STN DBS was not applied for the first time, but after 12 h OFF stimulation in patients already receiving DBS for at least 3 months. In this condition, one cannot exclude that plastic changes may have already occurred and that a 12 h OFF period is not long enough to reverse such adaptations. In the experimental behavioral studies reported later (see Sections 3.2.1 and 3.2.2), we have noticed that STN HFS peak effect was observed after a few sessions of 30 min stimulation (Baunez et al., 2007; Darbaky et al., 2003). As for the OFF effect, we also observed that the first few sessions exhibited a residual effect of DBS on behavioral performance. It is therefore important to take this into account when comparing studies carried out during several days with those where parameters change from one session to the next, with no consideration of this effect.

Because changes occurring at the electrode–brain interface level can affect the response to stimulation, a sham implantation effect cannot be excluded, either short- or long-lasting. Thus, comparisons in experimental animals should be made between stimulated and sham-implanted, rather than with non-implanted. Interestingly, and in agreement with this issue, several clinical reports have mentioned significant improvements after initial implantation of the electrode before turning ON electrical stimulation. These reports include, for example, surgery at the level of the ventrocaudalis thalamic nucleus for the treatment of chronic neuropathic pain (Hamani et al., 2006), the inferior thalamic peduncle in a patient with resistant major depression disorder (Jimenez et al., 2005), and the anterior thalamus in patients with intractable seizures (Hodaie et al., 2002). It is also to note that a strong placebo effect of DBS has also been reported, in which the outcome of the stimulation varies depending on the patient's expectation (Mercado et al., 2006). A recent long-term study (6 months) on PD patients showed a therapeutic benefit of electrode implantation alone, possibly resulting from disruption of cells and/or fibers within the penetrated region (Mann et al., 2009).

2.2.2. Electrode design

Size, shape and area of the microelectrode can affect the spatial distribution of the current density on the electrode surface and the electric field generated within the brain tissue, and overall affect brain tissue reactivity and potential neural damage (McIntyre and Grill, 2001). Tissue damage can be mostly attributed to electrode polarization and hydrolysis, which induces a dramatic change in tissue pH as well as production of gas. Moreover, in the presence of oxygen, these chemical reactions may include oxygen reduction and formation of reactive oxygen species, which are implicated in tissue damage (Bergamini et al., 2004).

Increasing the electrode tip radius results in a decreased magnitude of current density at the tip of the electrode for equivalent stimuli. However, there is not a strict correlation between geometric charge density and tissue damage. The current density distribution is nearly uniform along the surface of the electrodes when they have a large surface area ($>500\ \mu m^2$) with a blunt tip. The volume of tissue activated during the stimulation increases linearly with electrode height, while it decreases with increasing electrode surface (Butson and McIntyre, 2006). In conclusion, an electrode design with a low diameter/height ratio maximizes the volume of tissue that can be activated. However, electrode height must be limited to respect the frontiers of the targeted brain structure, and this is a major limiting factor in animal models, due to the small dimensions of brain structures. In humans, the implantable components consist generally of a

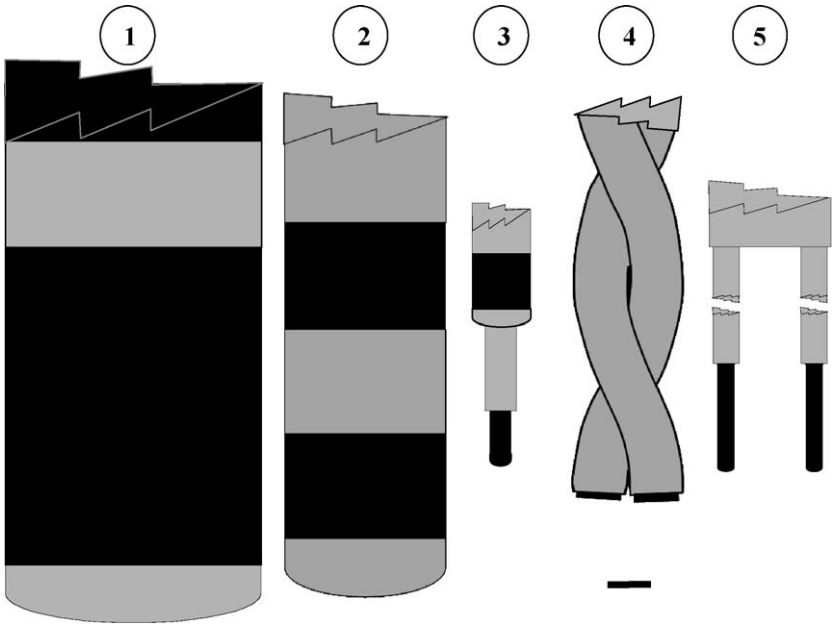

Fig. 1. Types of electrodes utilized for DBS. Schematic drawing illustrating the design of different bipolar stimulating electrodes commonly used for DBS in human (1), monkey (2) and rat (3 and 4). Note the differences in the size (scale bar = 200 μm) of the electrodes used in primates (5.98 mm^2 surface area contact) and rodents (0.07–0.18 mm^2 surface area contact), conditioning the differential threshold of safe current density allowed (the black areas represent the active parts of the electrode delivering current, the grey zones are the insulated parts). The drawing of electrode 1 shows the distal end (the last of the four electrode contacts) of the approved leads currently used in human DBS (Model #3389 from Medtronic, Inc.© company). Electrode 2 is a scaled-down version (diameter 0.70 mm vs. 1.27 mm; height of inner contacts 0.50 mm vs. 1.5 mm) of electrode 1. The design of electrode 3 corresponds to a commercial stainless steel electrode from Rhodes Medical, Inc. (SNE-100 and SNEX-100 with a 100 μm inner contact diameter; NE-100 and NEX-100 with 200 μm diameter have not been illustrated) used by the most studies of short DBS duration (see Table 1). Electrode 4 corresponds to the twisted stainless steel wire produced by Plastics ONE Inc.®, the active contacts being the cross-section of the two tips. Electrode 5 is the custom-made one used in our laboratory for chronic DBS in different brain structures of the rat (contact diameter 76 μm, height 500 μm; inter-contact distance 350–500 μm). The bipolar design of this electrode allows targeting a cerebral region in horizontal orientation (such as the STN), which can be useful to selectively stimulate small rodent structures in the antero-posterior or medio-lateral axis.

smooth 1.27 mm diameter by 28 (or 40) cm long urethane outer jacket having four annular platinum/iridium electrode contacts near the lead tip (Fig. 1). Each contact length along the lead axis is 1.5 mm, the inter-contact distance being 1.5 mm or 0.5 mm (models #3387 and #3389 respectively from Medtronic, Inc.®). The surface area of each DBS electrode contact is 0.06 cm^2 and the mean lead impedance is within a range of 400–1200 Ω. In non-human primates, the electrodes used are scaled-down versions of the human ones (Fig. 1). They consist of 1.2- or 0.76-mm diameter quadripolar stimulating leads with four cylindrical electrode contacts (Baup et al., 2008; Dorval et al., 2008); see also Table 1. In rodent models of DBS, the size and the shape of the electrode used strongly differ from those used in humans (Fig. 1). A large part of the DBS studies in rat used concentric bipolar stainless steel electrode type SNEX-100 (inner contact area 0.085 mm^2) or NEX-100 (inner contact area 0.19 mm^2) from Rhodes Medical Inc. However, although these stainless steel electrodes are appropriate for short duration stimulation, they are not recommended for chronic DBS because they are rapidly damaged (cathode degradation) and they induce histological lesions (Harnack et al., 2004b). For this reason, electrodes now used by research groups working on chronic DBS in animal models are made of platinum–iridium, essentially inert in brain tissue, as also those utilized in humans (Bacci et al., 2004a; Baunez et al., 2007; Boulet et al., 2006; Darbaky et al., 2003; Oueslati et al., 2007; Temel et al., 2005). Indeed, platinum is relatively non-toxic to the brain when compared to metals such as gold or rhodium. Most of the commercial bipolar electrodes have a vertical orientation of the cathode–anode axis. This could be a problem in rat brain structures, which mostly have a smaller ventro-dorsal vs. antero-posterior extent, so that the current field is likely to spread off the anatomical target. For this reason, we have developed an electrode design addressing this issue (Fig. 1).

2.2.3. Charge density and pulse waveform

Several studies have found that increased charge density at the electrode tip is associated with increased histological damage (Bullara et al., 1983; McCreery et al., 1990). The charge density (C/m^2) is the amount of electric charge Q in a surface or volume ($Q = I\,PW/A$; where I = current intensity, PW = pulse width, and A = electrode surface). In a clinical situation, it is considered that if the charge density exceeds 30 $\mu C/cm^2$/phase, there is a risk of tissue damage. Considering the usual electrode contact surface (0.06 cm^2), the current intensity must not go over 30 mA. This limit is much lower in animal models, since the surface of the inner contact of most electrodes used is around 6×10^{-4} cm^2 (Fig. 1), lowering the maximal safe current intensity below 0.25–0.35 mA. Indeed, one of the main problems in transposing DBS devices from human to animal models is the difference in size scale: compared to human brain, rat brain is around 1000-fold smaller and macaque's is 16-fold smaller. In the BG, for example, the volume of the STN is 300-fold smaller in the rat (0.8 mm^3) and 7-fold smaller (34 mm^3) in the macaque compared to human, and for the GPi the difference is even more important (Hardman et al., 2002). This issue requires miniaturizing the body of the electrode and thus the active surface of the lead, therefore reducing the maximal current intensity that can be applied without a potential risk of tissue damage.

As mentioned before, tissue lesion mainly depends on charge density, but it is also linked to electrode properties. With a same design and a same range of current intensity (around 150 μA), the stainless steel electrode after several hours or days of continuous DBS induces tissue damage, contrarily to platinum–iridium electrode (Harnack et al., 2004b). Using stainless steel electrodes, we also observed a deterioration of the electrode active pole with a loss of metal after several hours of continuous stimulation. It is worth noting that current intensities usually reported in literature

for STN HFS in awake animals are largely below the safe threshold, because severe side-effects are already observed from 150 to 200 μA, notably abnormal involuntary movements and rotational behavior (Bergmann et al., 2004; Boulet et al., 2006; Meissner et al., 2002; Oueslati et al., 2007; Salin et al., 2002). Interestingly, the induction of these hyperkinetic movements can be used to determine the stimulation parameters for each individual (Darbaky et al., 2003). However, numerous studies in anesthetized animals or *in vitro* preparations have used higher intensities for shorter periods.

The choice between biphasic and monophasic waveforms of the stimulation signal has been questioned in DBS procedures (as for electrical therapy for ventricular tachycardia or ventricular fibrillation). Indeed, stimulators can deliver monophasic pulses that induce current flow in one direction in the brain (cathode to anode), whereas others can deliver biphasic pulses in which the current is first induced in one direction and then in the opposite one (cathode–anode switch). The purpose of biphasic stimulation is to reverse the direction of the electrochemical processes that occur during the stimulation phase, minimizing the accumulation of unrecoverable charge. Upon delivering current in the stimulation phase and then reversing the direction of current in the following phase, the charge of electrode capacitance will also discharge, returning the electrode potential towards its pre-pulse value. In comparison, the monophasic stimulation protocol allows the electrode's cathode potential to remain relatively negative during the inter-pulse interval, and during this time faradic reduction reactions may continue. This, also depending on the electrode material, can ultimately increase the possibility of inducing tissue damage. Therefore, because they should be safer in terms of tissue damage induced by electrical stimulation, biphasic waveforms should be preferred over monophasic, even if the efficacy of the latter seems to be higher (Merrill et al., 2005).

Regarding pulse shape, the rectangular pulse waveform has been "historically" and commonly used for DBS in human and animal models. However, waveforms other than the perfect square wave have been recently proposed as more efficient alternatives (Merrill et al., 2005; Sahin and Tie, 2007): linear and exponential decrease and Gaussian waveforms were found to be the most efficient pulse shapes, maximizing the charge injection capacity of the electrode while providing the lowest threshold charge for neural activation.

2.2.4. Bipolar vs. monopolar stimulation

In humans, monopolar electrode stimulation is mostly applied since the limitation of current diffusion in a specific cerebral structure is not a restrictive clinical criterion. In addition, lower current intensity is needed for equivalent efficacy of DBS with monopolar vs. bipolar electrodes, thus saving the battery. For these reasons, despite the large and unknown diffusion across the brain in the direction of the reference electrode (localized on the microstimulator), monopolar DBS is favored. Indeed, the risk of current diffusion in human brain is minimized by the fact that the current density (A/mm^2) is inversely proportional to the square of the distance between the electrode tip and the neuronal elements (axon and soma), according to the inverse-square and Coulomb laws, suggesting that the current density decreases rapidly with the distance. Moreover, at far field, the current density needed to evoke an action potential from a neuron is dependent only on the neuron's distance from the electrode tip and on the amount of current delivered by a particular pulse duration, and is independent from the surface area of the electrode (Tehovnik, 1996). Regarding the spatial extent of brain tissue activation during DBS, it has been reported, for example, that DBS can activate areas up to 2–3.9 mm distance from electrodes placed in the thalamus (Kuncel et al., 2008), suggesting that the volume of tissue activated in clinical conditions could exceed the boundaries of the target structure. Furthermore, the heterogeneous conductivity of brain components (gray vs. white matters; extracellular fluid vs. cellular elements; fibers vs. cell bodies) suggests that the electric field can be more complex and does not respect the classic law of current diffusion. On the other hand, in experimental animal studies on DBS, the risk of current diffusion outside the specific target with monopolar electrodes is higher and must be taken into account, due to the smaller dimensions of the brain. This important issue restricts the use of monopolar stimulation when the objective is to determine the effects of DBS in specific brain structures, and argues for the use of bipolar electrodes with both tips localized in the target structure in animal studies.

2.2.5. Concluding remarks

In summary, change and/or damage in the tissue surrounding the electrode, electrode material and its possible degradation, charge density (that depends on electrode surface), and duration and waveform of stimuli can have a significant impact not only on the effect and the efficacy of DBS, but also on the safety of this method (Cogan, 2008; Harnack et al., 2004b; Merrill et al., 2005). Platinum electrodes should be preferred to stainless steel, and biphasic waveforms are preferable and safer than monophasic ones. The electrodes should be bipolar and DBS should be applied following a schedule that allows taking into account the possible time required to induce significant behavioral effects and possible remnant effects. Finally, horizontal current flow between the electrode tips following the antero-posterior or lateral axis is more appropriate than dorso-ventral.

2.3. Neurophysiology of DBS: lessons from STN HFS

Experimental studies on DBS developed in animal models have mainly focused on STN high-frequency stimulation (HFS). The observation that the surgical destruction of the STN could ameliorate parkinsonian motor symptoms suggested that STN HFS may act by blocking the electrical activity of this structure, thus functionally acting like a lesion. A short time after STN HFS started to be routinely used for PD in the early 1990s, parallel studies began characterizing its neurophysiological mechanisms and consequences in experimental models. Most of these studies have been performed with electrophysiological approaches in order to assess how STN HFS affects the intrinsic activity and properties of STN neurons, but also on how this treatment affects BG circuitry and the function of connected and surrounding structures (see Fig. 12 for a scheme of the BG). In this context, *in vitro* slice preparations are a very good option because they are able to better isolate the effects of HFS on neuronal properties. Behind *in vitro* techniques, the so-called *ex vivo* preparations include experimental models in which DBS is delivered *in vivo*, but the effects studied *in vitro* (in brain samples, brain slices, etc.). This approach provides a sort of "static picture" of the consequences of DBS on a given structure and/or parameter, but has the advantage over *in vitro* that HFS is delivered in the intact brain of a living animal, rather than on a slice that obviously lacks the whole brain connections (the other concern with *in vitro* studies is that they do not allow checking whether or not HFS has a functional efficacy). Moreover, *ex vivo* approaches give the possibility of easily performing investigations that would be technically impossible or extremely challenging if done *in vivo*. Although *in vitro* and *ex vivo* studies provide the possibility of characterizing the synaptic and membrane response to STN HFS, as well as other cellular and molecular changes, *in vivo* approaches are indeed necessary for investigating the widespread effects of DBS in the brain in terms of metabolism, neuronal activity, etc., as well as for assessing its functional outcome. On the other hand, many *in vivo* experiments,

in particular electrophysiological ones, are performed under anesthesia (commonly used anesthetics are chloral hydrate, urethane and halothane); in considering such studies, two important factors must be taken into account: (i) anesthetics can affect *per se* the activity of neurons (Mahon et al., 2001, 2003), and halothane has also been shown to affect glutamate release (MacIver et al., 1996); (ii) the electrophysiological activity of neurons is dependent on the waking state of the animal (Mahon et al., 2006). Therefore, the use of anesthetics affects neuronal activity not only by their direct pharmacological action (which is poorly characterized), but also because neurophysiological features of asleep animals are different from those of awake ones.

2.3.1. Electrophysiological properties of STN neurons

The STN belongs to the so-called "indirect pathway" of the BG and also to the "hyperdirect pathway" (see Fig. 12). STN is a glutamatergic structure innervating mainly the output structures of the BG, i.e., the GPi [entopeduncular nucleus (EP) in rodents], and the substantia nigra pars reticulata (SNr). In addition, the STN also projects to the GPe (GP in rodents) and the ventral pallidum (VP), the pedunculopontine nucleus (PPN), the striatum and the nucleus accumbens (NAc), and the dopaminergic nuclei, including the ventral tegmental area (VTA) and the SNc. Its major inputs originate in various cortical areas (i.e., hyperdirect pathway), in the VP and GPe (the "indirect pathway" from striatum), in the parafascicular nucleus of the thalamus, in the PPN, dorsal raphe, VTA, and SNc (Parent and Hazrati, 1995a, 1995b), and recent evidence for a direct STN–cortex loop circuit in the rat has been provided (Degos et al., 2008).

The electrophysiological and membrane properties of STN neurons have long been characterized *in vitro* by several groups (Beurrier et al., 1999, 2000; Bevan and Wilson, 1999; Nakanishi et al., 1987; Overton and Greenfield, 1995; Yung et al., 1991). These cells are spontaneously active and fire action potentials (APs) at the resting membrane potential (RMP) or when they are depolarized. The frequency of APs at RMP is variable, ranging from less than 10 Hz up to 20–25 Hz, depending on the recording condition and on the RMP value. When depolarized by strong current injection, these cells can reach spike frequencies up to 300–500 Hz. Approximately half of the STN neurons have a spontaneous and tonic firing activity, also called "single-spike" mode (Fig. 2A). The other half can switch from tonic to burst-like firing pattern, or "burst" mode. This switch is voltage-dependent, the burst mode being triggered by hyperpolarizing the neurons at about −42 to −60 mV, while at potentials around −35 to −50 mV the firing pattern reverses to single-spike. At membrane potentials more hyperpolarized than −60 to −70 mV most STN neurons are silent (Fig. 2B). Two types of burst-firing patterns have been observed in STN neurons: a "pure" burst mode consisting of regular burst-firing episodes separated by short quiescent periods, and a "mixed" burst mode consisting of long bursts separated by sequences of short bursts (Fig. 2C). Other authors have classified these three cell types as "normal" or "tonic", "bursting" or "phasic", and "mixed" or "phasic–tonic", respectively (Hollerman and Grace, 1992; Magarinos-Ascone et al., 2002). Single-spike activity of STN neurons is a spontaneous pacemaker-like activity, which is insensitive to antagonists of AMPA and NMDA glutamate receptors and $GABA_A$ receptors, blockers of Ca^{2+} currents (such as Co^{2+} or Ni^{2+}), or intracellular Ca^{2+} chelators (such as BAPTA). This means that it is independent from synaptic afferences and Ca^{2+}or Ca^{2+}-activated currents. Single-spike activity mainly results from two depolarizing cationic currents: the so-called persistent Na^+ current (I_{NaP}) that activates below spike threshold and inactivates slowly, and the hyperpolarization-activated cation current (I_h), which contributes in maintaining RMP at depolarized values (Beurrier et al., 2000; Bevan and Wilson, 1999; Nakanishi et al., 1987). Burst

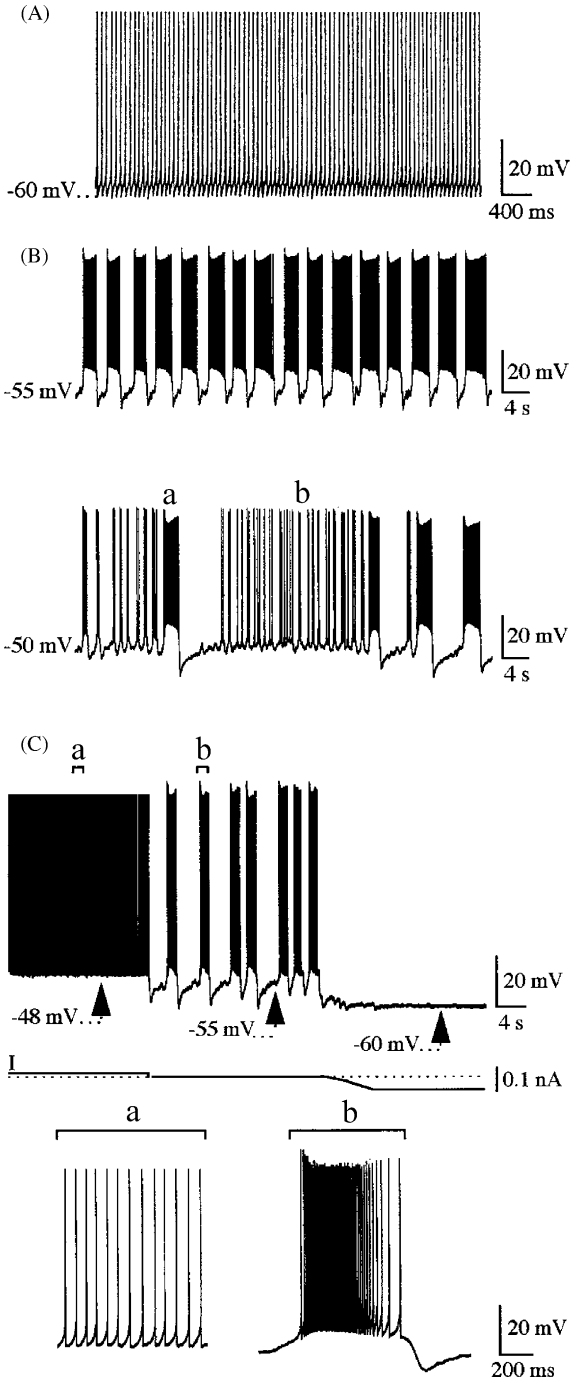

Fig. 2. Spontaneous firing properties of STN neurons recorded *in vitro*. (A) Tonic and regular activity of a STN neuron: single-spike mode (mean inter-spike interval 66.1 ± 15.6 ms). (B) Two types of burst mode: pure burst mode (upper trace) and mixed burst mode (lower trace) consisting in long bursts (a) separated by sequences of short bursts (b). (C) Firing mode switches from single-spike (a) to pure burst mode (b) by hyperpolarizing the neuron from −48 to −55 mV. At more hyperpolarized potentials (−60 mV) all spontaneous firing activity is suppressed [used with kind permission and modified from Beurrier et al., 1999, Copyright © (1999) The Society for Neuroscience].

mode activity results from phases of cyclic and alternate activation/inactivation of depolarizing and hyperpolarizing currents (Fig. 3). The voltage-dependence of the currents implicated in the generation of this activity is presumably also responsible for the switch between firing modes (single-spike to burst mode) of STN neurons (Beurrier et al., 1999). However, also synaptic mechanisms seem to be involved in the regulation of STN neuron activity: Bevan et al. (2002a) have shown that GABAergic input

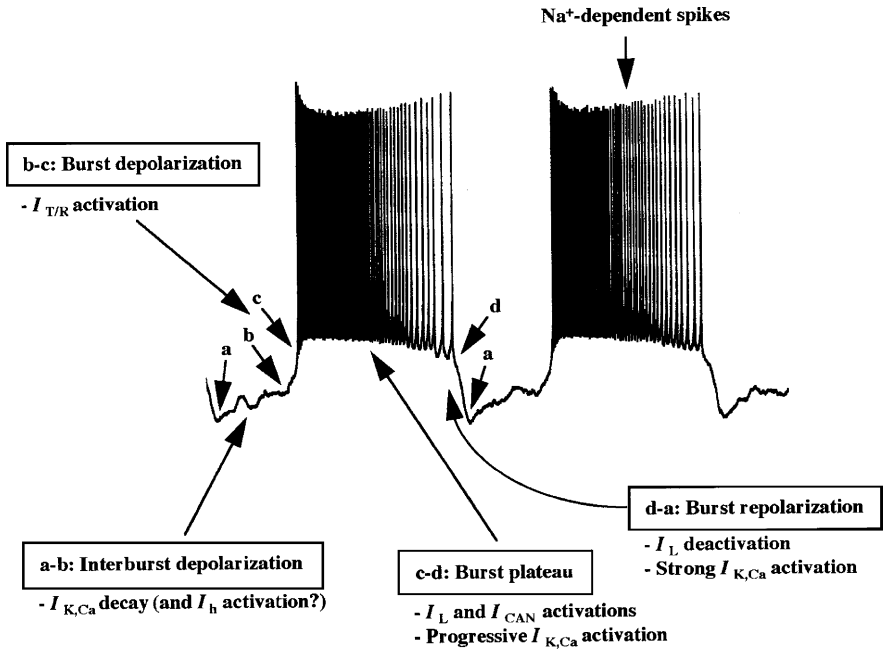

Fig. 3. The hypothetical cascade of currents underlying the different phases of burst-firing mode. The depolarization phase (b–c) results from a low-threshold T/R-type Ca^{2+} current ($I_{T/R}$) that depolarizes the membrane to the threshold potential of L-type Ca^{2+} current (I_L) and then inactivates. The slowly inactivating I_L depolarizes the membrane to the plateau phase, during which spikes are evoked (c–d). Spikes amplify Ca^{2+} entry by activating more I_L and, possibly, other types of high-threshold Ca^{2+} currents (such as the non-specific cationic current, I_{CAN}). The resulting increase in intracellular Ca^{2+} concentration activates the Ca^{2+}-activated K^+ currents ($I_{K,Ca}$). The balance between depolarizing (I_L) and hyperpolarizing ($I_{K,Ca}$) currents, slightly in favor of the latter, explains the gradual decline of the plateau towards the repolarization phase. When membrane potential has declined to a certain level, it suddenly repolarizes (d–a) because of rapid I_L deactivation and stronger $I_{K,Ca}$ activation. This leads to the peak of after-hyperpolarizing potential (a), during which $I_{T/R}$ activates, leading to a new membrane depolarization (a–b) as $I_{K,Ca}$ decays because of Ca^{2+} clearance mechanisms. The depolarization to the threshold potential of $I_{T/R}$ thus initiates a new cycle of the burst mode. A hyperpolarization-activated cation current (I_h) may also participate in the slow depolarization (a–b) between two consecutive bursts [used with kind permission and modified from Beurrier et al., 1999, Copyright © (1999) The Society for Neuroscience].

from the GP interplays with membrane properties of STN neurons to produce different patterns of firing, which is in contrast with the above findings. Another study suggests that the activity pattern of STN neurons could also be regulated by an opposing influence of D1- and D2-like dopamine (DA) receptors (Baufreton et al., 2005).

Since STN is presumed to become hyperactive in PD, several studies have addressed this issue by performing electrophysiological recordings in experimental PD models. Those performed *in vivo* in rats with 6-OHDA lesion in the SNc provided quite contradictory data on the AP frequency and discharge pattern of STN neurons (Hassani et al., 1996; Hollerman and Grace, 1992; Kreiss et al., 1997; Ni et al., 2001a, 2001b; Tai et al., 2003; Vila et al., 2000). This could be due to the different kind of anesthesia utilized, which can affect the basal firing activity of these cells. More homogeneous data arose from recordings performed in awake monkeys treated by MPTP: the spontaneous firing rate is slightly increased and the percentage of neurons showing burst activity is also enhanced. Periodic oscillatory neuronal activity at low frequency (which in humans is highly correlated with tremor) has also been detected in a large proportion of STN neurons after MPTP treatment (Bergman et al., 1994; Bezard et al., 1999; Meissner et al., 2005). Oscillatory patterns in the low (β) frequency range are recorded in parkinsonian patients and are thus presumed to be associated to this disease and the consequent limb tremor (Bergman et al., 1998a, 1998b; Bevan et al., 2002b, 2006; Boraud et al., 2002; Brown et al., 2001; Brown, 2003, 2006; Kuhn et al., 2004; Levy et al., 2000, 2002; McAuley and Marsden, 2000; Williams et al., 2002).

2.3.2. Effects in the STN and mechanisms

2.3.2.1. In vivo electrophysiology. The first report showing the electrophysiological effects of STN HFS on STN neurons was provided *in vivo* in urethane-anesthetized rats by Benazzouz et al. (2000b), showing that, after 5 s of DBS, the activity of these cells was inhibited for 30–90 s. The same group (Tai et al., 2003) lately investigated DBS effects in unilaterally 6-OHDA-lesioned rats. In parkinsonian animals, STN neurons showed no average change in the mean firing rate compared to controls, while the percentage of irregular firing STN neurons increased. DBS was delivered at 130 Hz for 10 s and current intensity was considered below the threshold for the induction of dyskinetic movements and contralateral rotations. In both control and 6-OHDA rats, a significant inhibition or suppression of the firing rate was observed during DBS in the majority of STN neurons (Fig. 4A). Interestingly, this group also utilized low-frequency stimulation (LFS) at 1, 10 and 50 Hz, showing that the response to DBS is frequency-dependent: the higher the frequency, the higher the percentage of neurons showing changes in their spike activity. A similar inhibitory effect on STN neuron activity has been provided by Shi et al. (2006b) in behaviorally active rats with unilateral 6-OHDA lesion. In their study, STN HFS was delivered by 3 s "ON-" and 2 s "OFF-stimulation" cycles during 20 s treadmill walking phases, in which the locomotion impairments due to 6-OHDA lesion were improved by DBS. STN HFS induced a decrease in the firing rate in 62% of the recorded STN neurons ipsilateral to the stimulating electrode, and in 26% of contralateral, while few cells showed an increased discharge rate. However, the use of ON/OFF stimulation cycles prevented the observation of effects lasting more than 2–3 s, and it can be argued that such cyclic stimulation has no equivalent in other papers or in clinical application.

The effect of STN HFS on the activity of STN neurons has also been investigated in primates by several groups. For example, Meissner et al. (2005) utilized two rhesus macaques treated by MPTP, in which the efficacy of DBS was confirmed by measuring contralateral rigidity on a modified Unified Parkinson's Disease

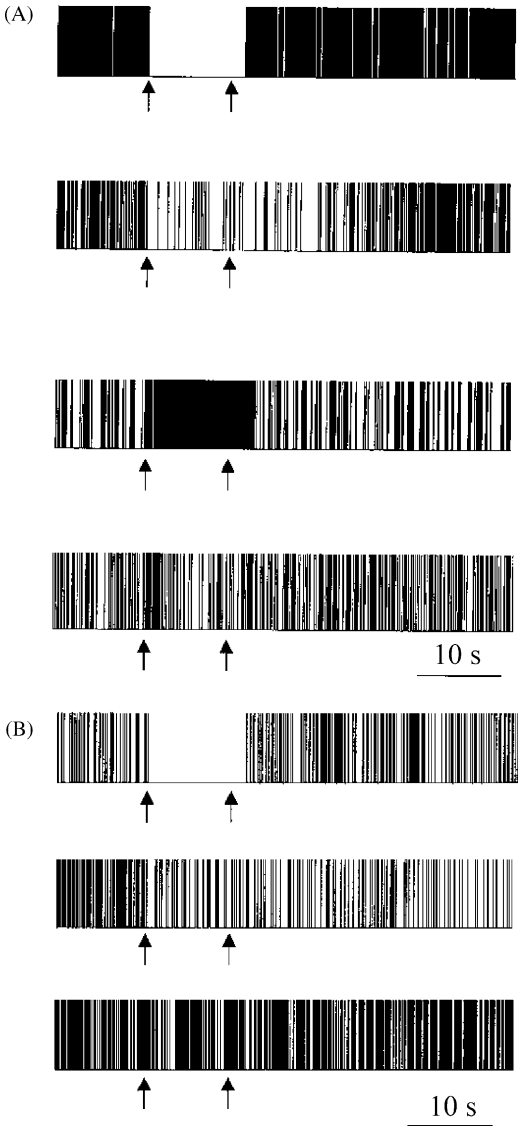

Fig. 4. Single-unit extracellular recordings of STN and SNr neurons *in vivo*. (A) Raster displays representing a typical example of each of the four types of response observed in STN neurons during 130 Hz STN HFS (period between arrows). From above: complete inhibition, partial inhibition, excitation, and no change. (B) Raster displays representing a typical example of each of the three types of response observed in SNr neurons during STN HFS. From above: complete inhibition, partial inhibition, and no change. Arrows represent the beginning and the end of the HFS period [used with permission and modified from Tai et al., 2003].

Rating Scale (UPDRS, multiple ratings that measure motor function, and also mental functioning, behavior, mood, and activities of daily living). Each recording session included 6 min before, 6 min during and 9 min after stimulation. The mean spike frequency of STN neurons was not significantly affected by MPTP lesion, in contrast with previous data showing increase of spike frequency and of the number of neurons with a burst discharge pattern (Bergman et al., 1994; Bezard et al., 1999). Similar to what was observed in 6-OHDA lesioned rats (Benazzouz et al., 2000b; Tai et al., 2003) and in PD patients (Filali et al., 2004; Welter et al., 2004), the firing rate of STN neurons in the macaques was inhibited by STN HFS. Another interesting report of Meissner's work, however, is that the spikes triggered by STN HFS were not time-locked to the electrical stimulus, which is quite the opposite of what was observed *in vitro* (see below). Another reported effect was the decrease in the number of oscillations of individual STN neurons, but without affecting their oscillation frequency (in the τ and α band). Since abnormal oscillations of the cortico-BG-cortical loop are presumed to play a role in the motor symptoms of PD (Brown, 2003), their reduction by STN HFS may represent a mechanism by which this therapy is beneficial for the treatment of this pathology.

2.3.2.2. In vitro electrophysiology. The first report showing *in vitro* the effect of STN HFS was provided by Beurrier et al. (2001), who performed electrophysiological patch-clamp recordings from rat slices. The spontaneous firing activity of STN neurons was blocked after HFS, and this effect was clearly frequency-dependent, because at frequencies of 166–250 Hz the blockade was total, but at 100–125 Hz some spike activity was spared (Fig. 5). Such inhibitory effect was similar in neurons with single-spike activity and in those with bursting activity; it was reversible (spike activity recovered after ~6 min), and HFS could be repeated several times with the same effect, as long as the recording lasted. The mechanisms of this inhibition seem to rely on the reduction of Na^+ and Ca^{2+} voltage-gated currents and to be independent from the activation of $GABA_A$ or ionotropic glutamate receptors. Magarinos-Ascone et al. (2002) completed this *in vitro* characterization by analyzing what actually occurs during HFS (100–130 Hz) by using specific signal filtering and analysis procedures. Intracellular recordings showed that a steady membrane depolarization was induced by HFS: this depolarization initially triggered AP failures, followed by high-frequency spike activity during the first 5–10 s of HFS, and then by burst activity until the neuron was silenced after 15–20 s of stimulation. At lower frequencies (70–90 Hz), HFS also induced a stable depolarization with initial AP failures, followed in few seconds by a persistent burst firing that lasted until the end of the stimulation. A similar increase in AP firing during STN HFS, followed by inhibition, was also reported by Lee et al. (2003) in rat slices, where STN HFS could trigger excitatory postsynaptic potentials (EPSPs) and increase the frequency of AP discharge, or vice-versa trigger inhibitory postsynaptic potentials (IPSPs) and decrease AP frequency; these effects were blocked by GABA and glutamate receptor antagonists (Lee et al., 2004). This is surprisingly in contrast with the above findings by Beurrier et al. (2001), thus a possible role of synaptic inputs to STN cannot be completely excluded to explain the effects of HFS.

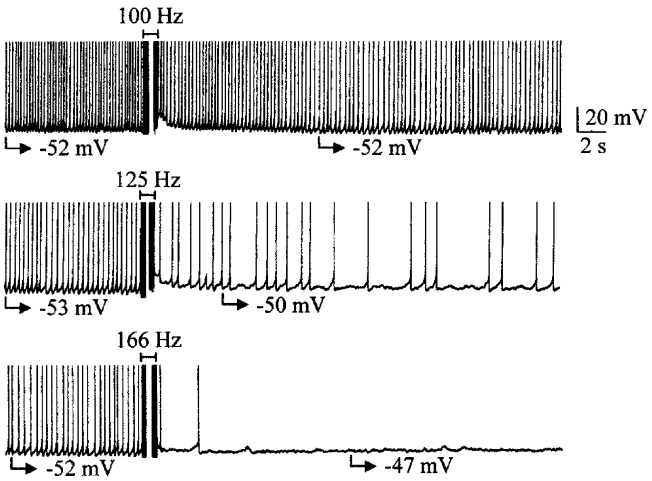

Fig. 5. Post-effect of STN HFS on the firing activity of STN neurons *in vitro*. The traces are from the same STN neuron with single-spike firing mode. Applied at 100 Hz (upper trace), HFS has nearly no post-effect, whereas at 125 Hz (middle trace) it decreases the frequency of tonic activity, and at 166 Hz (lower trace) stops single-spike activity for 5 min [used with permission from Beurrier et al., 2001].

Longer stimulation times (30 min to 2 h) were studied by Garcia et al. (2003, 2005b) in slices from an acute rat model of PD (DA depletion by i.p. injection of reserpine and α-methyl-*p*-tyrosine) and from control rats (the effects of STN HFS were similar in the two groups). At 10 Hz, HFS was unable to affect STN neuron activity even at high stimulation intensity, and at 30 Hz only some cells showed a reduction of spontaneous activity. Conversely, at 50 and 80 Hz, STN neuron spontaneous firing was completely replaced by a stimulation-driven activity at the same frequency of stimulation. At 130 and 185 Hz the frequency of evoked spikes could not follow that of HFS, but it was driven at roughly half of the stimulation frequency (Fig. 6). When HFS was turned off, STN neurons remained silent for a period variable from 20 s to 8 min, similar to what was described previously by Beurrier et al. (2001). Thus, only HFS delivered at therapeutic range frequency (80–185 Hz) seems able to replace the spontaneous firing activity by a stimulus-driven one. However, it can be argued that in these papers the parameters of pulse duration and intensity were adjusted to obtain an electrophysiological response rather than to stick to clinical relevance.

Overall, these reports on STN neuron activity during HFS (Garcia et al., 2003, 2005b; Magarinos-Ascone et al., 2002) support the concept that DBS disrupts the abnormal synchronized activity recorded in the BG–thalamocortical loops in parkinsonian state (Hammond et al., 2007), but only when delivered with parameters that are able to suppress burst activity and impose a tonic pattern. However, beside frequency, stimulation parameters are not equivalent to what is applied in clinical conditions and in *in vivo* studies.

2.3.2.3. Synaptic and metabolic changes induced by STN HFS. Besides the effects of STN HFS on the firing activity of STN neurons, another interesting issue was to characterize how this treatment affects other parameters within this structure. Shen et al. (2003) studied the effects on glutamatergic synaptic transmission by stimulating the rostral STN and recording the evoked excitatory post-synaptic currents (EPSCs) from STN neurons (patch-clamp technique on slices). Three different forms of synaptic plasticity were obtained after HFS in STN neurons: (1) 9% short-term potentiation (STP) of glutamatergic EPSCs, associated to a decrease in paired-pulse ratio (PPR); (2) 17% long-term potentiation (LTP) without changes in PPR; (3) 11% long-term depression (LTD) associated to PPR

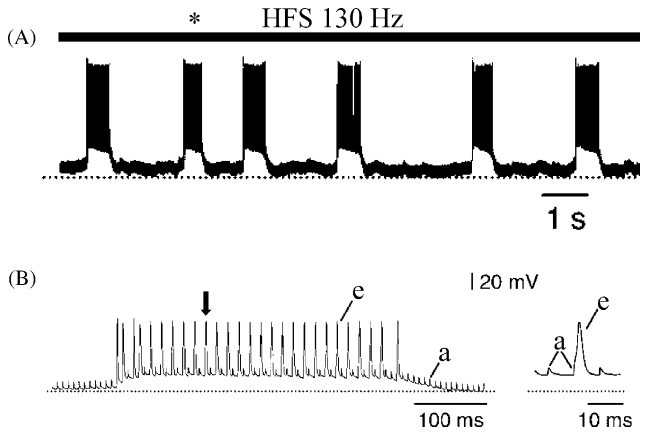

Fig. 6. Firing activity of STN neurons during STN HFS *in vitro*. (A) Electrophysiological recording of burst activity of a rat STN neuron during HFS at 130 Hz applied continuously for 30 min. (B) On the left, the expanded trace of the burst marked with * in (A), showing evoked spikes (e) and stimulation artifacts (a). Note that, during the burst, the frequency of the evoked spikes is roughly half of that of artifacts, i.e., not all stimuli can trigger an action potential. The spike indicated by the arrow is expanded on the right. Note the two artifacts (a), one preceding and the other triggering the spike [used with permission and modified from Garcia et al., 2005b].

increase. The authors suggested that STP could be due to a transient increase of glutamate release, while LTD to a decrease (as suggested by PPR increase). Conversely, LTP maintenance should more likely depend upon postsynaptic mechanisms. This work was the first showing plastic changes evoked by STN HFS at glutamatergic synapses on STN neurons, and brings several intriguing findings. In fact, while HFS-induced LTD is consistent with the "classical" view of an inhibitory action of DBS on the STN, HFS-induced LTP conversely supports an excitatory action of DBS, as also suggested by several studies that will be presented below. This work thus suggests that STN HFS does not simply inhibit STN output, but it also induces complex and contrasting synaptic changes within this nucleus. In this context, we showed that STN HFS applied for 2 h in normal and parkinsonian awake rats induced c-Fos expression specifically in the stimulated STN, which is in agreement with an increased neuronal activity (Salin et al., 2002). A recent study in anesthetized control rats (Schulte et al., 2006) confirmed our results and further showed that STN HFS applied for 4 h also induced c-Jun and Krox-24 expression in stimulated STN neurons. This immediate early gene induction suggests that HFS indeed modifies the activity of STN neurons, but is unable to inform us univocally about the nature of HFS influence on these neurons, i.e., inhibitory or excitatory. To further address this question, we measured mRNA expression of cytochrome oxydase subunit 1 (COI), which is the terminal enzyme of the mitochondrial electron-transport chain. Its expression level is correlated to neuronal metabolism (Hevner et al., 1995; Wong-Riley, 1979), and modifications of COI mRNA expression in different BG nuclei have been shown to correspond to changes in neuronal firing rate and pattern (Hirsch et al., 2000). Our studies and others reported that STN HFS decrease COI mRNA in the stimulated STN in naïve rats, or reversed its increase induced by DA lesion (Bacci et al., 2004a; Benazzouz et al., 2004; Salin et al., 2002; Tai et al., 2003). Since the increase of metabolic activity in STN neurons after DA lesion is correlated with a change of their firing pattern (from a regular pattern of discharge to a bursting activity), such decrease of COI mRNA expression in the STN under HFS could reflect the reduction of the firing observed by electrophysiological studies (Benazzouz et al., 2000b; Tai et al., 2003). Regarding the consequences of STN HFS on glutamate concentration, Lee et al. (2007) used an electrochemical sensor to show that it was quickly increased in the STN and then decreased slowly towards baseline after cessation of stimulation (5–60 min). These data argue against the hypothesis that DBS works primarily by electrotonic inhibition of the stimulated structure, at least for the STN.

About the metabolic effects of STN HFS, Meissner et al. (2007) studied 2-deoxyglucose (2-DG) uptake in MPTP monkeys. These authors showed that DA lesion induced a decrease of 2-DG accumulation in the STN, which was reversed by chronic STN HFS lasting for 10 days. It is still not clear the significance of 2-DG uptake in terms of excitatory or inhibitory influence and cellular elements involved. However, this study concluded that STN HFS could normalize the abnormal responses of BG structures to DA lesion: it is proposed that the reversal of 2-DG increase triggered by HFS might reflect the activation of inhibitory GABAergic inputs to the STN that could counteract the post-lesion STN hyperactivation.

2.3.3. Effects on the pallidal complex and mechanisms

The first study on the effect of STN HFS on its target structures was performed in the anesthetized rat by Benazzouz et al. (1995), who monitored the activity of pallidal neurons before and after 5 s stimulation. STN HFS induced a clear-cut decrease in neuronal activity in 80% of the recorded EP neurons, while it activated 100% of GP cells. It should be mentioned that the time-course of the inhibition recorded in the EP was longer than that of the time-course of behavioral or clinical effects reported in MPTP-treated monkeys

(Benazzouz et al., 1993) and in parkinsonian patients (Pollak et al., 1993). The authors suggested that such differences might be attributed to the fact that rats were anesthetized by chloral hydrate, compared to normally behaving monkeys and patients, but the fact that they stimulated for only 5 s might also be responsible for these differences. Another study on the effects of STN HFS in the GP of parkinsonian rats has been provided by Shi et al. (2006b), who recorded extracellularly from ipsi- and contralateral GP (see above for the ON/OFF stimulation protocol). In average, less than 20% of ipsi- and contralateral GP neurons responded to DBS. Among those that responded, the majority showed inhibitory responses during the 3 s "ON-stimulation" period. Neurons showing excitatory responses exhibited a rebound excitation during the 2 s "OFF-stimulation" period (8.3%) or during the 3 s "ON-stimulation" period (6.7%). Overall, however, no significant changes in firing rate were triggered in the GP by STN HFS.

The primate is probably the most suited model to study the widespread effects of STN HFS with an electrophysiological approach. Hashimoto et al. (2003) examined the effects of DBS on parkinsonian motor signs, not only in order to assess the efficacy of this treatment, but also to find the effective stimulation parameters. In both monkeys, 136 Hz DBS could ameliorate contralateral spontaneous limb movement and rigidity, without inducing dyskinesia. At 136 Hz and higher, the second stimulus of a given couple of stimuli coincided with the later components, giving rise to a wave parameter in four phases (inhibition–excitation–inhibition–excitation). The overall result was that STN HFS changed the spontaneous firing of GPe and GPi neurons from an irregular to a high-frequency regular pattern (Fig. 7). Stimulation usually lasted 30 s, during which a run-down of the average frequency was observed, but longer DBS periods (>5 min) revealed that the increase in the mean discharge rate lasted during the whole stimulation (Fig. 7). On the other hand, LFS (2 Hz) produced a short-term response in pallidal neurons consisting in a wave of five consecutive inhibition and excitation components. Furthermore, Dorval et al. (2008) measured firing pattern entropy in two MPTP-treated rhesus monkeys (a decrease in firing entropy reflects a more orderly firing pattern, and vice versa) during STN HFS. These authors showed that HFS (136 Hz) decreased entropy in both GPe and GPi, where neurons responding to STN HFS showed spikes that were phase-locked to the stimulation pulses. In contrast, LFS (2 Hz) had the opposite effects. On the other hand, a recent study raised some doubts on a direct correlation between the motor effects of STN HFS and its consequences on pallidal neuron activity (Hahn et al., 2008). These authors showed that, during HFS, the mean firing rate increased both in the GPe and GPi, while burst rate (the number of bursts occurring each minute) increased in the GPe and decreased in the GPi. However, although such changes were significant in only one animal, both of them showed improvements of the parkinsonian motor symptoms.

Biochemical studies in the EP of parkinsonian rats showed that STN HFS (lasting 2 h or 3 days) partially reversed the increase of GAD67 (enzyme of GABA synthesis) mRNA due to 6-OHDA lesion. Conversely, STN HFS applied for 3–6 days, but not 2 h, antagonized the increase of GAD67 mRNA in the GP induced by 6-OHDA lesion (Bacci et al., 2004a; Salin et al., 2002). Altogether, these results show an inverse time-course of HSF effects in the two pallidal nuclei, suggesting a possible network plasticity of the pallidal complex under stimulation. It is to note that Meissner et al. (2007) showed an increase of COI expression in GPi in MPTP monkeys after 10 days STN HFS, suggesting that a longer period of stimulation would, on the contrary, increase GPi activity. Moreover, they also showed that DA lesion induced an increase of 2-DG accumulation in the GPi and GPe, which was reversed by chronic STN HFS lasting for 10 days. Such increase of 2-DG may be due to the hyperactivity of excitatory input from the STN on these two structures, and the reversal of these

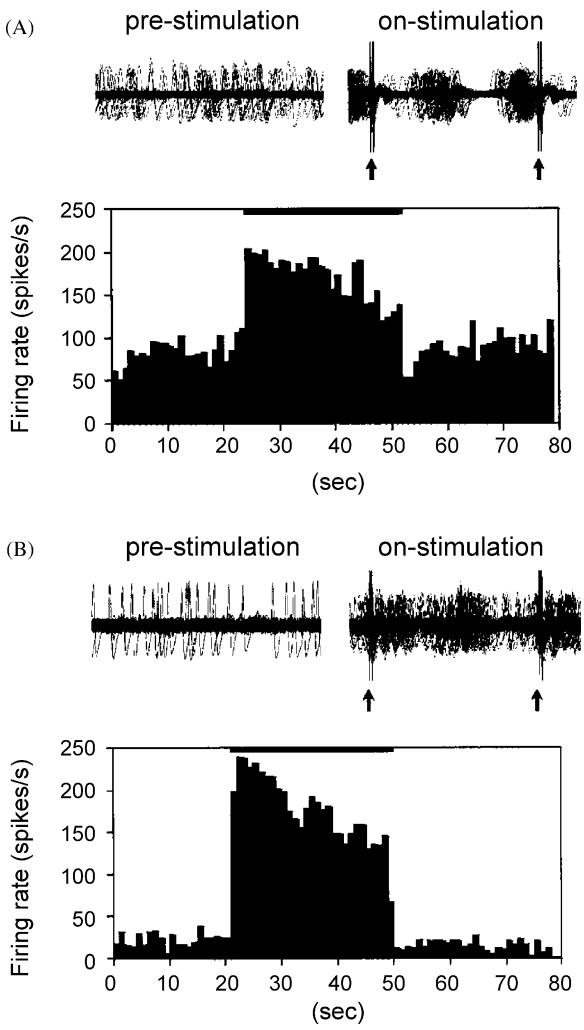

Fig. 7. Neuronal responses of GPe/GPi to STN HFS in the rhesus monkey *in vivo*. Traces are 10 ms sweeps of neuronal activity of a GPi (A) and a GPe (B) neuron, before and during DBS at 136 Hz (black bar). Arrows represent the residual stimulation artifacts. Note how neuronal activity is increased and, more notably, regularized, by STN HFS. The plots show the mean firing rate (calculated every 1 s) before, during and after STN HFS: firing activity increases immediately when DBS is turned on and then progressively runs down during stimulation [used with kind permission and modified from Hashimoto et al., 2003, Copyright © (2003) The Society for Neuroscience].

enhancements under HFS could reflect the reduction of STN activity by the stimulation, as already shown by other studies (Bacci et al., 2004a; Salin et al., 2002; Tai et al., 2003).

In summary, STN HFS seems to have an effect on the activity of pallidal neurons, but the effect is different between the rat and the primate model: while in the former model neurons respond by reducing their firing activity both in EP and GP, in the latter model, spike activity increases and becomes more regular both in GPi and GPe. Further work seems thus necessary to better understand the action mechanisms of STN HFS at the level of the pallidal complex.

2.3.4. Effects on the SNr and mechanisms

In the above-mentioned paper by Benazzouz et al. (1995), the effect of 5 s STN HFS was also studied on firing activity of SNr neurons of rats (anesthetized with chloral hydrate). They reported that the activity of the vast majority of SNr cells was reduced after stimulation, with a longer time-course compared to behavioral or clinical effects observed in MPTP-treated monkeys and in parkinsonian patients. As mentioned above for the EP, such differences could be attributed to anesthesia or to the short

duration of the stimulation. These results were later confirmed in the SNr of both control and 6-OHDA lesioned rats (Benazzouz et al., 2000a, 2000b; Tai et al., 2003).

Using longer stimulations (30 s), Maurice et al. (2003) showed during STN HFS ~65% of SNr neurons were inhibited (Fig. 8A), while ~22% were excited (Fig. 8B) in rats anesthetized by chloral hydrate. Interestingly, this inhibitory vs. excitatory effect was correlated with, respectively, stimulation intensity below and above 4 V. Low-intensity stimulation induced an inhibition by increasing GABAergic transmission in the SNr, while higher intensity stimulation elicited an excitation, likely resulting from the activation of the subthalamonigral pathway. Another interesting finding was that ~13% of SNr neurons were antidromically activated by STN HFS at all stimulation intensities, and the antidromic spike followed with high fidelity the stimulation at 130 Hz, up to 600 Hz. In contrast with the above findings, Shi et al. (2006b) showed that around 40% of SNr neurons were affected by STN HFS, with an equal amount of excitatory and inhibitory effect during the "ON" phase, but their procedure using very short cycles of ON/OFF stimulation might not allow the measurement of reliable physiological effects.

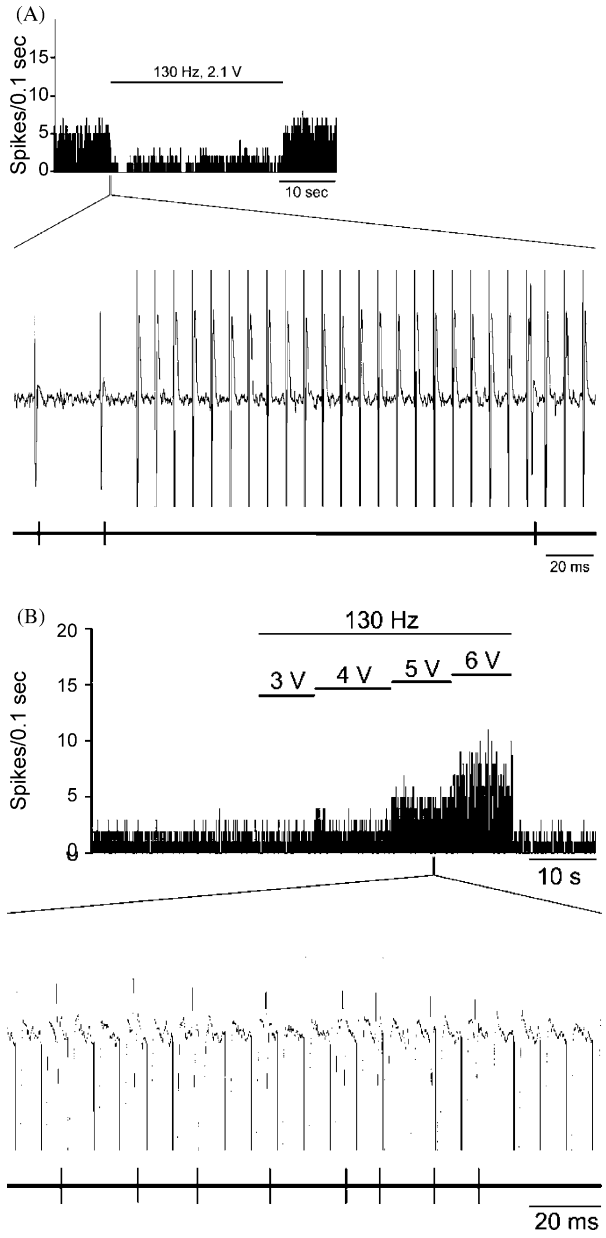

Fig. 8. Inhibitory and excitatory effects of STN HFS in the rat SNr *in vivo*. (A) Rate histogram illustrating the decreased spontaneous firing of a SNr cell during STN HFS (130 Hz); horizontal line indicates the time of application of STN stimulation. Lower traces show a magnified view of the recording (top trace) depicting the onset of STN HFS and of the event channel (bottom trace) confirming that only spikes were sampled. (B) Rate histogram illustrating the increase of firing of a SNr cell during STN HFS (130 Hz) at the intensities and duration indicated by horizontal lines; note that the excitatory effect is elicited only during the application of HFS at high intensity. Lower traces show a magnified view of the recording (top trace) and of the event channel (bottom trace), confirming that only spikes were sampled [used with kind permission and modified from Maurice et al., 2003, Copyright © (2003) The Society for Neuroscience].

An alternative rat PD model is catalepsy induced, for example, by a mix of D1- and D2-like receptor antagonists. Degos et al. (2005) injected SCH-23390 and raclopride in order to induce such cataleptic state in rats, which was accompanied by an altered discharge mode of SNr neurons. Both tonic and regular firing became irregular and exhibited high-frequency bursts of spikes and/or pauses. Moreover, these DA antagonists also induced an imbalance between the influence exerted on the SNr by the direct and indirect striatonigral circuits: when stimulating the cortex, the inhibitory component of the response evoked in SNr cells via the direct striatonigral pathway was reduced, whereas the late excitatory component resulting from the activation of the indirect trans-striatal pathway was increased. Interestingly, during STN HFS (applied at behaviorally efficient parameters) SNr neurons were either inhibited or activated (the net effect was an overall increased activity) but, in both cases, their firing pattern was regularized. Moreover, STN HFS restored the balance between the inhibitory and excitatory influence over the SNr exerted by the direct striatal pathway and the trans-subthalamic inputs, respectively. These data suggest that the action mechanism of STN HFS at SNr level is mainly based on restoring the spatiotemporal organization of SNr neuron discharge activity, rather than simply reducing their overactivity.

Further support for the idea that STN HFS may act by normalizing SNr neuronal activity came from several biochemical studies. For example, the increase of GAD67 and COI mRNA expression in the SNr, detected after DA lesion, was suppressed by STN HFS (Bacci et al., 2004a; Benazzouz et al., 2004; Salin et al., 2002; Tai et al., 2003). These data can be correlated with the early gene induction in SNr neurons after STN HFS that was, however, delivered on intact animals (Schulte et al., 2006). Moreover, microdialysis studies showed that STN HFS induced an increase of extracellular GABA contents in the SNr of hemiparkinsonian anesthetized rats (Windels et al., 2005). Such enhancement of nigral GABA levels by STN HFS could thus underlie the reduction of SNr activity both in control conditions and in PD models. In summary, STN HFS seems to induce a decreased neuronal activity within the SNr that might be mediated by an increased GABAergic input, presumably originating from pallidonigral fibers.

2.3.5. Effects on the striatum and mechanisms

Few studies addressed the impact of STN HFS on striatal neurons. We showed that short duration (hours) or prolonged (days) STN HFS did not affect the increase of preproenkephalin mRNA and the decrease of preprodynorphin and preprotachykinin induced in the rat striatum by DA lesion (Bacci et al., 2004a; Oueslati et al., 2007; Salin et al., 2002), suggesting that this stimulation fails to normalize the metabolism of striatal output neurons. On the other hand, we reported that 5 days STN HFS could dramatically reduce spontaneous glutamatergic activity (Fig. 9), recorded *ex vivo* (corticostriatal slices) from medium spiny neurons of 6-OHDA-lesioned rats, treated or not with L-DOPA (Gubellini et al., 2006). Interestingly, such effect was paralleled by a significant improvement of akinetic symptoms assessed by the cylinder test. It is known that glutamatergic activity in the striatum recorded *in vitro* is increased by 6-OHDA lesion (Gubellini et al.,

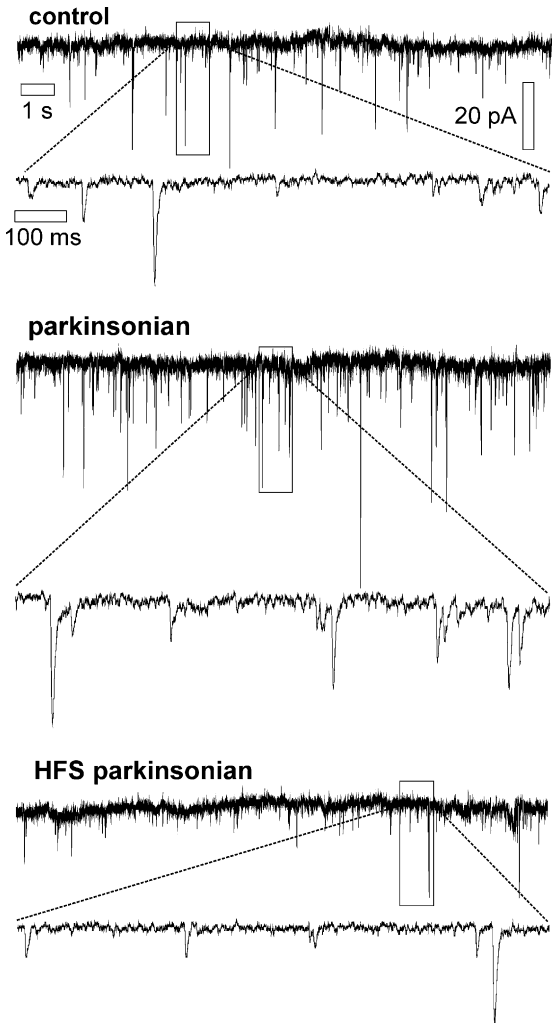

Fig. 9. Long-term effects of STN HFS on corticostriatal synaptic transmission. The traces show spontaneous glutamatergic activity recorded *in vitro* from three striatal MSNs: the upper one from a naïve rat (control), the middle from a 6-OHDA-lesioned (parkinsonian) rat, and the lower from a 6-OHDA-lesioned rat treated by 5 days chronic STN HFS (HFS parkinsonian). For each group, upper trace is a 16 s recording period, while the lower trace is an expansion of the period showed in the box. HP = -80 ± 5 mV for all depicted cells. Note that, compared to control, parkinsonian MSN shows a higher sEPSCs frequency and amplitude. STN HFS greatly reduces such glutamatergic hyperactivity [used with permission and modified from Gubellini et al., 2006].

2002, 2006), and *in vivo* data seem to support this finding (Tseng et al., 2001). Thus, these changes of corticostriatal glutamate transmission seem to correlate with 6-OHDA-induced akinesia. It should be mentioned that glutamatergic hyperactivity and akinesia induced by 6-OHDA lesion were also reversed by STN lesion (Centonze et al., 2005), suggesting that similar mechanisms might underlie the motor and synaptic effects of STN lesion and STN HFS. Taken together, our data suggest that while chronic STN HFS can modulate the activity of striatal neurons, this does not result in parallel metabolic changes in these cells assessed by neuropeptide expressions. It is possible that such changes occur in a time window different from that during which electrophysiological measurements were performed. However, these findings clearly show that STN HFS also affects the striatum, although this structure is not a major target of the STN. Accordingly, Shi et al. (2006b) also showed that about 30% of ipsi- and 15% of contralateral striatal cells responded to DBS with an equal amount of excitation and inhibition. We have also recently recorded *in vivo* single-unit firing activity of striatal neurons in sham and hemiparkinsonian rats (unilateral 6-OHDA lesion) by means of four tetrodes implanted in the dorsal striatum. Chronic STN HFS was delivered ipsilaterally to the recording electrode bundle during 5 days, and the recordings were performed during OFF stimulation in freely moving rats. Our preliminary data showed that, in hemiparkinsonian animals, STN HFS progressively lowered spike frequency of striatal neurons and altered their firing pattern, the latter switching towards a burst mode (i.e., spikes tended to be at an overall lower frequency and more concentrated into bursts). Interestingly, DBS had no such effects in sham animals, suggesting that DA loss might be necessary for STN HFS to affect spike activity striatal neurons (Gubellini et al., 2008). While at this time these data need to be confirmed, they further support the role of striatal neuron activity in the action mechanisms of STN HFS.

As the striatum is the main target of nigral DA projection, several studies addressed the effects of STN HFS on the BG DAergic system and on its projection in the striatum. STN HFS was shown to increase striatal DA efflux in rats with partial DA lesion (Bruet et al., 2001; Lee et al., 2006; Meissner et al., 2003), and reversibly increase extracellular levels of 3,4-dihydroxyphenyl-acetic acid and homovanillic acid, two DA metabolites, in the ventral striatum of 6-OHDA-lesion rats (Winter et al., 2008b), suggesting that this treatment could promote DA transmission via the VTA-NAc pathway. Taken together, these results suggest that an enhanced DA release could be a mechanism whereby STN HFS improves motor symptoms at early stages of PD. However, whether STN HFS improves PD symptoms at late stages via the release of DA remains a matter of debate, and it is unlikely, due to the massive loss of DAergic neurons. To date, positron emission tomography (PET) studies carried out in PD patients with STN HFS failed to show any effect on raclopride binding (Strafella et al., 2003), but a stabilization of DA concentration in the striatum that may alleviate L-DOPA-related motor fluctuations has been reported (Nimura et al., 2005). Beside striatal DA transmission, it has been reported that STN HFS increases extracellular glutamate and GABA levels in the striatum, and that this response seems to be modulated by DA (Bruet et al., 2003), suggesting again that the action mechanisms of STN HFS may also involve structures that are not direct STN targets.

2.3.6. Effects on other targets and mechanisms

2.3.6.1. PPN. PPN is reached by a contingent of STN output fibers that, although less numerous than those projecting to the SNr and GP, may have a relevant role in mediating the positive motor effects of STN HFS (Jackson and Crossman, 1983; Nauta and Cole, 1974; Parent and Smith, 1987). For this reason, Florio et al. (2007) investigated the effect of STN HFS in the PPN of rats anesthetized by chloral hydrate. These authors classified PPN neurons in three groups according to their firing properties: type 1 (39.7%), showing a rather regular firing pattern; type 2 (44.9%), with an irregular activity; type 3 (15.4%), with an oscillatory activity consisting in alternate periods of bursts and silences. 6-OHDA lesion reduced the number of type 1 neurons, decreased the mean activity of type 2 and had no effect on type 3. STN HFS in control rats affected 39.4% of PPN neurons, of which 84.6% were inhibited and 15.4% activated just after the end of the stimulation period. Such inhibition/activation lasted, respectively, around 4–15 s and was not dependent on the duration of the stimulation. On the other hand, one-third of the inhibited neurons were activated during HFS. The percentage of PPN neurons responding to DBS (35.4%) was not affected by 6-OHDA lesion, and again the main result of STN HFS was the inhibition of neuronal activity in 90.9% of the recorded cells, similar to control rats.

2.3.6.2. Ventral nuclei of the thalamus. In the above-mentioned paper, Benazzouz et al. (2000b) also examined the effects of STN HFS in the ventrolateral nucleus of the thalamus of anesthetized

rats. Neurons of this structure responded with a significant increase in their activity, which also lasted for 25–150 s after DBS was turned off. Another study, addressing the effects of brief periods of STN HFS on thalamic structures in MPTP-treated primates, showed that it could reduce neuronal firing entropy (i.e., regularized firing pattern) in the pallidal receiving area of the motor thalamus (ventralis anterior and ventralis lateralis pars oralis) and in the cerebellar receiving thalamus (ventralis posterior lateralis pars oralis); conversely, LFS had the opposite effect (Dorval et al., 2008). Moreover, the same group also showed that behaviorally effective STN HFS inhibited neurons of the pallidal receiving thalamus, while exciting those of the cerebellar receiving thalamus (Xu et al., 2008). Overall, these data suggest that STN HFS increases STN output and regularizes the firing pattern of the neurons of thalamic nuclei, inhibiting those receiving pallidal afferences and exciting those receiving cerebellar inputs.

2.3.6.3. Dorsal raphe nucleus. The dorsal raphe nucleus (DRN) is a midbrain structure providing extensive 5-hydroxytryptamine (5-HT) innervation to the limbic forebrain. The rationale for such a study is that STN HFS may inhibit the activity of DRN neurons, resulting in a decreased release of 5-HT into the limbic forebrain, and thus triggering psychiatric disorders, as mentioned before. In this context, Temel et al. (2007) have performed extracellular recordings from the DRN of anesthetized rats undergoing bilateral DBS of the STN, both in control and parkinsonian state (6-OHDA lesion). The neurons recorded from DRN have the characteristic slow and regular (0.7 ± 0.1 Hz) firing pattern of 5-HT cells. Bilateral STN HFS inhibited by 45.1% the firing activity of more than 90% of DRN neurons. This effect had a rapid onset during DBS and quickly reversed to baseline after turning off the stimulation. Interestingly, such inhibition occurred at stimulation parameters relevant to clinical application, i.e., at $\geq$100 Hz and 30 μA, but not at $\leq$50 Hz. In parkinsonian rats the basal firing frequency of 5-HT neurons was increased, and STN HFS also inhibited 5-HT cell firing by 52.4%, similar to what observed in control animals. Interestingly, the intra-STN injection of muscimol, a $GABA_A$ receptor agonist, mimicked the inhibitory effect of STN HFS on 5-HT neurons, suggesting that STN HFS may act by reducing STN output.

2.3.6.4. Cortex. A possible action of STN HFS could occur through the antidromic activation of the axon collaterals of cortical pyramidal neurons projecting to the STN, thus stimulating local cortical circuits. This hypothesis has been explored by Li et al. (2007) in the rat, both in control and in parkinsonian state. Intracellular recordings showed that a small group (15.6%) of layer V/VI cortical neurons responded to STN HFS with an antidromic spike, whose frequency reflected that of DBS and with a latency of ~2 ms (Fig. 10A and B). The other group of cells, while not being directly activated by STN HFS, was modulated in terms of membrane potential: the overall effect was a significant reduction of the hyperpolarized state during DBS, with also a marked reduction of depolarization/hyperpolarization potentials. A possible mechanism could be that antidromically stimulated neurons activate local excitatory and inhibitory cortical networks, thus dampening the slow wave up-down activity typical of the anesthetized rodent. The excitation due to DBS reached the deep cortical layers with a delay of ~2.5 ms, then spread to the more superficial layers within the following ~5 ms. Electroencephalographic (EEG) recordings showed that a single stimulating pulse delivered to the STN triggered two positive peak responses, separated by a gap of ~8.5 ms, the first with ~2.8 ms latency from the stimulation (Fig. 10C). Thus, at DBS frequency around 100–120 Hz, in which the inter-stimulus interval is around 8.5 ms, each stimulus occurred exactly at the time when the two peaks originated, resulting in a resonant superimposition of the primary

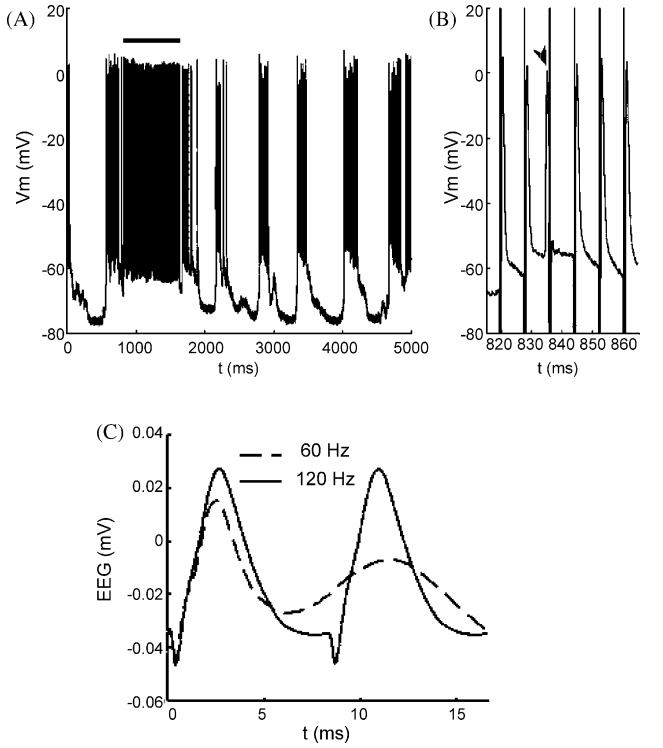

Fig. 10. Antidromic activation of motor cortex by STN HFS. (A) Example of an *in vivo* intracellular recording from a rat motor cortex neuron, depicting the antidromic activation by STN HFS. (B) Close-up of (A) (see time scale) showing how spikes shortly follow DBS artifacts (2.0 ± 0.5 ms latency). The arrowhead shows a spontaneous spike that inhibits (by collision) the antidromic spike expected after the stimulus. (C) Comparison between averaged EEG responses to DBS at different frequencies (2.6 ± 0.5 ms latency). Note that at 120 Hz stimulation, the initial response is superimposed to the secondary response seen at 60 Hz, and the resulting initial response amplitude is increased, leading to a resonant response [used with permission and modified from Li et al., 2007].

peak of a given stimulus with the secondary peak of the preceding stimulus. STN HFS was also able to dampen the slow-wave EEG oscillations recorded from rats under deep anesthesia. The δ, τ, α, and low β bands were actually depressed during stimulation periods, and this effect was consistent with the above described antidromic activation of cortical areas. These findings further support the idea that cerebral cortex is involved in the mechanisms of action of STN HFS delivered at 100–120 Hz, as proposed by several studies in patients showing that STN stimulation produces evoked potentials in the frontal cortex (Ashby et al., 2001; Baker et al., 2002), and that direct stimulation of the motor cortex alleviates parkinsonian symptoms in both primates and humans (Drouot et al., 2004; Lefaucheur et al., 2004). Both the enhanced EEG responses and firing rate observed by Li et al. (2007) during short periods of DBS showed a rapid run-down during longer stimulation periods (100 s), which, however, reached a steady state at roughly 30% of the initial potentiation, suggesting that such effects of DBS can operate for longer periods of time. A very recent paper reported that STN HFS significantly reversed the increase in the power of β oscillations in the EEG of awake cataleptic rats (Dejean et al., 2009). Interestingly, stimulation resulted in a short latency (presumed antidromic) evoked potential in the cortex, which was paralleled by a significant rescue of motor function, with the level of akinesia (bar test score) being inversely correlated to the amplitude of the evoked potential. These studies confirm that cortical responses to STN HFS occur in the awake animal, that these responses are associated with reduction in abnormal cortical oscillations characteristic of PD, and that they result in akinesia improvement. It is to keep in mind that, besides antidromic

mechanism, STN HFS action at cortical level could also involve the recently identified direct subthalamo-cortical projection (Degos et al., 2008). Finally, further support for the action of STN HFS at cortical level has been provided by our cellular study measuring COI mRNA levels as a marker of neuronal metabolic activity in motor cortical areas (Oueslati et al., 2007). Analysis was performed after 5 days of continuous STN HFS in freely moving rats, focusing on pyramidal layer V neurons. STN HFS with a significant anti-akinetic effect could totally reverse the decrease in the metabolic activity of these neurons produced by DA lesion.

2.3.6.5. Dopaminergic and neuroprotective effects. Several *ex vivo* studies have been done to evaluate the potential effect of STN HSF on the survival of DAergic neurons, testing the hypothesis that silencing STN activity by HSF could be neuroprotective in PD. Maesawa et al. (2004) showed that STN HFS applied continuously for 2 weeks in the rat, prior to partial DA lesion induced by intrastriatal 6-OHDA injection, reduced DA neuronal loss. However, this study is not clinically relevant since HFS preceded DA lesion, whereas STN HFS in humans is performed when dopaminergic degeneration is ongoing. Alternatively, a recent report showed that bilateral STN HFS applied 1 h per day, starting a week after 6-OHDA injection and during a period of 3 months, increased the survival of midbrain DA neurons in rats. HFS had a protective effect on the number of DA neurons, as well as on the total number of neurons in the SNc (cresyl violet staining), suggesting a real neuronal sparing and not a change of tyrosine hydroxylase neuronal phenotype (Temel et al., 2006b). Accordingly, a recent study in rats using an implantable microstimulation system and taking into account the possible sham-effect due to electrode implantation showed that continuous STN HFS, applied for 2 weeks and initiated 5 days after 6-OHDA lesion, preserved 30% of nigral neurons expressing tyrosine hydroxylase (Harnack et al., 2008). Another study also indicated that STN HFS provided 20–24% neuroprotection to dopaminergic cells in MPTP-treated monkeys (Wallace et al., 2007). Moreover, Meissner et al. (2003) reported that STN HFS increased striatal tyrosine hydroxylase activity without affecting its gene expression, and enhanced striatal tyrosine hydroxylase activity by increasing its phosphorylation (Reese et al., 2008). Electrophysiological data showed that STN HFS influences the activity of SNc dopaminergic neurons by increasing their firing rate, and that this increase of activity is independent from the GP (Benazzouz et al., 2000a). Moreover, several neurochemical studies have evidenced an increased striatal DA transmission in response to STN HFS (Bruet et al., 2001; Lee et al., 2006; Meissner et al., 2002, 2003).

In conclusion, most of the studies in animal PD models or in control animals are in agreement with an activation of dopaminergic transmission by STN HFS. Taken together, these data suggest that STN HFS in early stages of PD might both exert a neuroprotective effect and limit DA depletion, possibly by increasing the activity and metabolism of the spared neurons. However, there is no clinical evidence supporting such mechanism, and it has even been reported that STN HFS failed to improve DA outflow in PD patients (Hilker et al., 2003; Thobois et al., 2003). Moreover, this mechanism is unlikely to participate to the therapeutic action of DBS in late PD stages, when patients usually undergo HFS, due to the already extensive DAergic neuron loss.

An important issue concerns the interaction between STN HFS and L-DOPA treatment: usually, a PD patient has been receiving dopaminergic treatment during several years before undergoing DBS, and this treatment can continue in parallel with STN HFS. To address this issue, we showed that 5 day STN HFS exacerbated striatal neuropeptide mRNA expression produced by L-DOPA treatment, including the responses that are sustained after L-DOPA withdrawal (Oueslati et al., 2007). Moreover, STN HFS has been shown to prolong the increase in striatal DA induced by acute L-DOPA treatment in 6-OHDA rats (Lacombe et al., 2007).

2.3.6.6. DNA expression. A recent study has investigated the effects of STN HFS applied for 3 h on a large screen of gene expression in sagittal brain sections including BG structures, by using DNA micro-array technique (Henning et al., 2007). It reported a decrease of Ca^{2+}/calmodulin-protein kinase type IIA and Homer1, suggesting a potential reduction of glutamate transmission in BG network. This study also showed that IGF2 and insulin-like growth factor binding protein 2 (IGFBP2) are increased after HFS, which would underlie a possible reorganization of the neuronal BG circuitry.

2.3.6.7. Bilateral effects of unilateral STN HFS. We have shown that with long duration of stimulation (4 days), unilateral STN HFS on the side of the DA denervation induced a bilateral decrease in COI mRNA levels in the STN (Bacci et al., 2004a). Bilateral responses in the STN to unilateral stimulation were further confirmed electrophysiologically by Shi et al. (2006b), as described above. These data provided the first substrates for the clinical observation that unilateral DBS produces bilateral benefits in patients with PD (Tabbal et al., 2008), which is suggestive of complex inter-hemispheric adaptive mechanisms. We also found that, in contrast with the appearance of a contralateral response in the STN, the changes in the expression of activity-related genes in the striatum, GP, EP and SNr remained restricted to the side ipsilateral to DBS and DA depletion. Whether or not the reduced neuronal metabolic activity of the STN contralateral to HFS can trigger contralateral functional changes in the BG network is an interesting issue to be further investigated, with possible insights onto the clinical effects of unilateral STN surgery for the treatment of PD.

2.3.7. Concluding remarks

The debate around the inhibitory vs. excitatory effect of STN HFS is exciting and all data indicate that while the activity of STN itself seems to be inhibited, still the consequences of this treatment are more complex and widespread in the brain. What seems to emerge from *in vitro* electrophysiological studies is that HFS disrupts the pacemaker-like activity of STN neurons by acting on the intrinsic membrane properties of these cells. If we stick to stimulation frequencies relevant to clinical use, this will result in a temporary inhibition of STN firing after brief (seconds) stimulations and also, and most importantly, in a more complex phenomenon during longer periods of HFS (minutes to hours): a complete replacement of spontaneous STN activity by a stimulus-driven one. Mechanisms involving changes in synaptic transmission within the STN can also play a role in these effects. On the other hand, it should be noted that all these *in vitro* electrophysiological studies were performed on very young or postnatal animals in which the structural and functional development of the brain synaptic network is still ongoing. It would be interesting to test whether in slices from adult rodents similar results can be obtained. Finally, no major differences in the effects of STN HFS emerge between parkinsonian and control animals. This is potentially interesting, since it implies that HFS could bypass the BG dopaminergic system and exert its effects directly on neuronal activity in the BG. If one could reply that slices lack the connectivity of the whole brain, surprisingly similar findings were confirmed by *in vivo* reports, although not with the same parameters for STN HFS.

Delivering STN HFS on living animals has revealed to be technically challenging and opened several new questions. For example, the application of this technique to a small animal such as the rat imposed miniaturizing the electrodes and finding materials that were suitable for such application. The result was, especially

for the rat, that several studies were performed utilizing bipolar electrodes, rather than monopolar ones such as those for clinical use and in primates. Concerning the stimulation parameters, *in vivo* studies have provided a major contribution for defining the range of current intensity that is behaviorally effective, clinically relevant and, in particular, not inducing motor troubles by itself. In fact, it is worth mentioning that HFS delivered above intensities of 100–200 μA (by both mono- and bipolar electrodes, and depending on electrode material) can trigger a dyskinetic-like motor behavior (Bacci et al., 2004a; Boulet et al., 2006; Salin et al., 2002; Tai et al., 2003). Thus, it is of extreme importance to keep appropriate stimulating parameters not only in terms of frequency (around 130 Hz), but also in terms of intensity. The current density is also an important parameter when one wants to compare animal models to human studies. Current density is defined as the intensity of the current vs. the surface of the electrode. Indeed, the active surface of the electrodes used in animals is smaller than those used in human, thus it is crucial to apply intensity lower than human studies, in order to prevent any tissue damage, as well as to be aware of the material constituting the electrode (Harnack et al., 2004b). Finally, most of the *ex vivo* and *in vivo* studies have been done in anesthetized animals and for short periods of stimulation (seconds to minutes): unfortunately, these experimental conditions do not allow checking if the current intensity applied induces behavioral effects and electrolytic lesions if applied chronically.

The effects of STN HFS on brain structures other than the STN itself are complex and intriguing. Regarding the cortex, its deep layers can be antidromically activated by HFS and modulated through direct subthalamo-cortical projections, resulting in changes in waveform activity patterns that could possibly affect both pyramidal and extrapyramidal pathways. Other brain structures that are anatomically correlated to the STN, such as the striatum and the SN, seem to be generally inhibited, while the GP provided contrasting results. Another interesting finding of electrophysiological *in vivo* and *ex vivo* studies is that they confirm what has been reported by the few electrophysiological *in vitro* works performed in PD models, i.e., STN HFS has some similar effects in parkinsonian and control animals. This is true for its direct effect in the STN itself, as well as for some changes in other brain structures examined. Again, as mentioned before, this could imply that STN HFS can bypass dopaminergic systems to exert its effects in the BG, at least at cellular level. However, the cellular mechanisms of this effect are still unknown. In the BG structures, whether some effects of STN HFS could be explained by a reduction of the excitatory STN influence, biochemical and electrophysiological data suggest that this issue is more complex. It could involve, for example, pallidal GABAergic transmission for the impact of HFS in the SNr, as well as differential effects of HFS in the preferential targets of the STN (GP and SNr). We now can assume that STN HFS induces a real reorganization of the BG network, including neuroplasticity phenomena such as structural and functional changes, fiber sprouting and connectivity rearrangements. Finally, several evidences support the hypothesis that STN HFS can disrupt the abnormal synchronized oscillatory activity of the subcortical–cortical loops in parkinsonian state, thus restoring a more physiological functioning of these structures and improving motor symptoms.

2.4. Mechanisms of DBS: clinical evidences

Human studies on the effects and mechanisms of DBS have been generally performed in PD patients during electrode implantation. Obviously, ethical and clinical constraints limit this approach but, on the other hand, non-invasive analysis systems such as PET provided new information that is not yet available in experimental models.

2.4.1. Target location for DBS

Implantation of DBS electrodes in patients is a complex neurosurgical procedure. The techniques vary greatly across centres, but in general they begin with stereotactic targeting of the brain structure to be stimulated, based on one or more imaging modalities such as ventriculography, computed tomography (CT) and/or magnetic resonance imaging (MRI). The large majority of these centres also utilize some form of electrophysiological mapping to define the optimal site, including microelectrode or semimicroelectrode recording, and microstimulation and/or macrostimulation testing, by using microelectrodes (>300 kΩ), semimicroelectrodes (<100 kΩ) or macroelectrodes (<1 kΩ, often the DBS electrode itself). Microelectrodes can record spontaneous and evoked single-unit neural activity and provide a high degree of spatial resolution, since they allow recognizing the target structure due to its neuronal firing properties and pattern. Stimulation can be performed with them, either at <50 μA for glass-insulated electrodes (microstimulation), or in the 100 μA range with more resilient non-glass-insulated electrodes, even up to the mA range (macrostimulation). The low amount of current delivered by microstimulation limits its capacity to evoke therapeutic responses, so this approach is generally not useful for testing clinical benefits. Semimicroelectrodes are used to record multiunit or local field activity, which can also be evoked. While providing less spatial resolution than microelectrodes, semimicroelectrodes are simpler to use and allow macrostimulation, which is useful to establish the location for the DBS electrode that is both safe and therapeutically effective. Macroelectrodes can be used to record larger EEG-type fields or tissue impedance, but provide very poor spatial resolution. Macrostimulation through macroelectrodes, including the DBS electrodes, is generally in the 1–10 mA range.

Postoperative imaging is often used to reveal possible hemorrhagic complications, grossly misplaced DBS leads that may require revision, and to provide insights that can guide future surgical interventions. These imaging techniques are the same as those used for the preoperative phase, with the difference that low field strength scans are recommended for MRI due to possible electrode or pulse generator movement or heating. Although most centres performing DBS surgery utilize some form of postoperative imaging to confirm lead location, to date it is not possible to draw conclusions as to the most accurate, safe and efficient technique (Gross et al., 2006; Rezai et al., 2006).

2.4.2. Neuronal single-unit activity

Among the first clinical reports on DBS effects in patients, some interesting data were provided by Dostrovsky et al. (2000) from three awake parkinsonian patients (12 h *off* L-DOPA medication) undergoing functional stereotactic surgery for GPi DBS. The spontaneous activity of nearly all of the recorded GPi neurons (22/23) was inhibited by DBS, the maximal effects being at 50–100 Hz, whereas the clinical effects were optimal only at >130 Hz. Microstimulation (5 Hz, 0.15 ms pulses, <10 μA) of the GPi led to firing inhibition lasting 10–25 ms following each pulse, suggesting that DBS probably activated inhibitory GABAergic afferents arising from GPe and putamen, leading to such inhibition of the output GPi neurons.

Regarding the STN, Filali et al. (2004) showed that STN HFS (100–300 Hz) resulted in the reduction of STN neuron firing in 25 of the 60 cells recorded from 12 PD patients 12 h *off* medication undergoing functional stereotactic procedures. Similarly, single-unit recordings obtained by Welter et al. (2004) in awake PD patients (>12 h *off* medication) showed a 77% inhibition of the 21 recorded STN neurons during STN HFS at 140 Hz, which persisted for several seconds after turning off stimulation (Fig. 11). In both cases, DBS was clinically effective in alleviating PD symptoms.

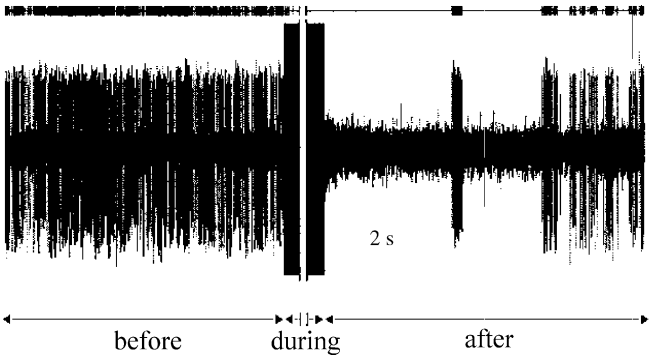

Fig. 11. Effect of STN HFS on STN neuron firing in a parkinsonian patient. Activity of a single STN neuron before, during, and after HFS within the STN. Note the presence of an inhibitory effect after STN HFS, followed by progressive resumption of neuronal activity [from Welter et al., 2004, Copyright © (2004) American Medical Association. All rights reserved].

Interestingly, these electrophysiological findings are in agreement with those obtained in the STN in experimental models.

Single-unit recordings of the SNr in awake PD patients (12 h *off* medication) showed that STN stimulation at 140 Hz decreased the mean firing rate of SNr neurons by 64% and the mean duration of bursting mode activity by 70%, while 14 Hz stimulation was not effective (Maltete et al., 2007). Interestingly, the residual SNr neuronal activity during STN HFS was driven by the stimulation itself, similar to what was observed experimentally in the STN, but not in the SNr. Conversely, Galati et al. (2006) reported that STN HFS (130 Hz) in awake PD patient (undergoing two sessions of electrode implantation and *off* medication since at least 10 days) caused a significant (~70%) increase of the SNr firing rate with an excitation peak regularly following the STN stimulus, so that the spontaneous discharge of SNr neurons was driven by HFS at the same frequency.

2.4.3. Local field potential

Several studies have provided interesting data from untreated PD patients using power spectra measurements from local field potential (LFP) recordings, showing a prominence of the β rhythm (10–30 Hz). Such exaggerated oscillatory synchronization in the β band frequency has been associated with bradykinesia in PD patients, giving rise to the fascinating "noisy signal hypothesis", based on pathological synchronization of the BG-cortical loop in terms of cell firing activity (Brown and Eusebio, 2008; Eusebio and Brown, 2007; Hammond et al., 2007; Marsden and Obeso, 1994). Thus, the inhibition of the abnormal and potentially deleterious synchronization of BG output could be the basis of DBS action mechanism. In this context, Brown et al. (2004) showed that stimulating the subthalamic area at ~20 Hz in two awake PD patients exacerbated β band synchronization in the GPi. In contrast, stimulating at >70 Hz suppressed such GPi β activity. Silberstein et al. (2005) further confirmed this hypothesis by cortical EEG recordings reporting that EEG coherence between different cortical areas (at approximately 10–35 Hz), which correlates with PD severity, was reduced by L-DOPA and STN HFS, and that such reduction correlated with clinical improvement of PD symptoms. These data were obtained from PD patients after overnight medication withdrawal and at least 2 months post-operatively.

Regarding the STN, some groups showed that its stimulation caused a significant and persistent (seconds) power attenuation in the β band in this nucleus in awake PD patients *off* dopaminergic medication (Kuhn et al., 2008; Wingeier et al., 2006), while others failed to report significant changes in the patterns of STN oscillatory activity before and after HFS (Foffani et al., 2006). Similarly, Rossi et al. (2008) showed that during ongoing STN stimulation the power of β oscillations remained unchanged in awake PD patients *on* and *off* levodopa, while the power of low-frequency oscillations (1–7 Hz) significantly increased, and such increase was boosted by L-DOPA. Thus, although some data supporting the "noisy signal hypothesis", this pathophysiological working model needs to be further tested and confirmed.

2.4.4. Microdialysis

Microdialysis measurements of extracellular neurotransmitter levels or activity-related molecules in the BG have generally reported, by different means, an activation of the stimulated structure. For example, elevated cGMP extracellular levels have been reported in the GPi (Stefani et al., 2005) and SNr (Galati et al., 2006) during clinically effective STN HFS for PD, supporting an increase of STN output to these structures. In line with this finding, Ogura et al. (2004) measured significant increases in GABA concentration in the cerebrospinal fluid of PD patients undergoing chronic and clinically effective GPi DBS, suggesting that such treatment may involve the activation of GABAergic afferents in the GP.

2.4.5. Functional imaging studies

PET studies measuring regional cerebral blood flow (rCBF) are based on the notion that rCBF and local metabolism are coupled to neuronal activity. Changes in rCBF are assumed to reflect changes in neuronal activity in target synaptic fields, including local interneurons and/or changes of the input to that region, rather than changes in efferent activity (Logothetis et al., 2001). Among the first PET studies during DBS, Goerendt et al. (2006) reported that the precentral gyrus, caudate and thalamus were activated by STN HFS in PD patients performing a spatial search task. Interestingly, the structures activated by DBS differed from those activated by L-DOPA treatment, while other brain regions (temporal gyri, anterior thalamus and midbrain) were activated by the two combined treatments, suggesting that DBS and L-DOPA may act through both common and different action mechanism. More recent studies focused on the effect of STN HFS on cortex by measuring ^{18}F-deoxyglucose (Le Jeune et al., 2008) or rCBF (Karimi et al., 2008) in PD patients: the former reported a decreased activity of the right orbitofrontal cortex, correlated with impaired recognition of facial emotions, and the latter a decreased activity of the right premotor cortex, as well as the bilateral thalami and right midbrain. Karimi et al. (2008) also found significant correlations between improvement of rigidity and decreased rCBF in the supplementary motor area, between improvement in bradykinesia and increased rCBF in the thalamus, and between improved postural reflexes and decreased rCBF in the PPN. The same group (Hershey et al., 2003) reported that bilateral STN HFS increased rCBF in midbrain (including STN), GP and thalamus primarily on the left side, but reduced it bilaterally in frontal, parietal, and temporal cortex (the lateralization of DBS effects seemed due to technical issues, and motor benefit was bilateral). These data are consistent with the hypothesis that STN HFS increases STN output, which in turn increases the inhibition of thalamocortical projections, ultimately decreasing cortical rCBF. Activation of the GP (and STN) during STN HFS was also reported by Hilker et al. (2008) in resting patients, while opposite results were obtained by Arai et al. (2008), who showed an increased metabolic decrease (^{18}F-deoxyglucose) in the contralateral GPi, but an increase in ipsilateral ventrolateral thalamic areas, during unilateral STN HFS. Another group reported, in PD patients at rest undergoing STN HFS, increases in rCBF in the pre-supplementary motor area, premotor and dorsolateral prefrontal cortex, primary motor/sensory cortex, GP, ventral lateral thalamic nuclei, cerebellum, pons, and midbrain entailing the SN (Sestini et al., 2005). A correlation was detected between the improvement in PD motor

scores and rCBF increase in the pre-supplementary motor area and premotor cortex. Such correlation between selective motor manifestations and rCBF in specific brain regions may underlie a regional selectivity for the improvement of different PD motor signs.

Few recent papers show the effect of GP stimulation on rCBF. For example, Payoux et al. (2009) reported that left GPe stimulation at rest, which could improve contralateral rigidity and akinesia, decreased rCBF in ipsilateral motor-related areas (cerebellum and lateral premotor cortex), but increased it in primary sensorimotor cortex during right hand movement. Thus, GPe stimulation seems to result in a reduced activity of motor-related areas and the facilitation of motor cortex activation during movement. In contrast, left ventral GPi stimulation, which improved rigidity but worsened akinesia, resulted in rCBF decrease in the left sensorimotor cortex and motor-related areas. Such rCBF decrease may thus be correlated to the worsening of akinesia by GPi stimulation.

A PET study carried out on patients at rest, implanted in the VIM for the treatment of essential tremor, showed that DBS increased rCBF in the motor cortex ipsilateral to the side of stimulation, while rCBF decreased in the right retroinsular (parietoinsular vestibular) cortex (Ceballos-Baumann et al., 2001). Such changes were triggered by 130 Hz DBS that was also clinically effective, but not by 50 Hz stimulation that was ineffective on tremor. Recently, Strafella et al. (2008) reported by PET analysis that unilateral PPN DBS (70 Hz) increased bilaterally rCBF in the thalamus of a PD patient at rest, resulting in 20% improvement in motor function.

Overall, these functional imaging studies show that DBS of a specific structure may affect widespread brain regions. However, they should be interpreted with caution for several reasons. For example, not all of them adequately assessed and considered behavioral condition of subjects during scan, which can affect measurements and rCBF. Moreover, the sample of PD patients that can be "utilized" for imaging is biased by the fact that the subjects showing either tremor or other movements extraneous from the behavioral task (or rest) are not included. Furthermore, when differences in the motor task are triggered by stimulation, then the resulting different sensory feedback might affect the metabolic rCBF response.

2.4.6. Adverse clinical effects of DBS

DBS has been reported to induce several adverse side-effects, the most important being acute and chronic behavioral changes (Anderson and Mullins, 2003; Voon et al., 2006). Acute changes are probably secondary to the direct effect of DBS on the target brain structure, involving adjacent structures and/or parallel circuitry. Chronic changes are probably also correlated to medication changes, neuronal plasticity following DBS, adaptation difficulties and dramatic socio-familial modification induced by the motor effects of DBS; they develop over months or years and may have severe consequences including suicide (Burkhard et al., 2004). For example, patients undergoing STN DBS for PD have been reported to develop depression (Berney et al., 2002; Houeto et al., 2002; Thobois et al., 2002), apathy (Krack et al., 2003), anxiety and pathological gambling (Houeto et al., 2002), mania (Kulisevsky et al., 2002), sexual disinhibition and hypersexuality (Romito et al., 2002), euphoria (Kumar et al., 1999b), hallucinations (Burn and Troster, 2004), and mood changes, which were also induced by GPi DBS (Okun et al., 2003). While acute effects can usually be corrected by tuning DBS, chronic modifications need to be detected and often necessitate a multidisciplinary approach to be managed.

Other serious adverse events usually and commonly reported in patients undergoing DBS include cerebral hemorrhage, infections and other troubles linked to surgery and other clinical issues (skin erosion, foreign body reaction, granuloma, seroma and pain over the pulse generator). Hardware complications are sometimes reported, such as DBS electrode fracture, extension wire failure, lead migration and stimulator malfunction (Rezai et al., 2006; Weaver et al., 2009). However, it must be emphasized that all these adverse effects of DBS surgery appear in an encouragingly low number of patients, thus they do not invalidate this technique, which still remains a useful, safe and effective approach for a multitude of neurological diseases.

3. Deep brain stimulation and Parkinson's disease

PD is a debilitating neurodegenerative movement disorder with a long course and a high prevalence (1–2 over 1000 individuals in the European Union) that increases with demographic ageing. It is widely accepted that the progressive loss of DAergic SNc neurons leads to the manifestation of the main symptoms of PD (muscle rigidity, tremor and bradykinesia/akinesia) due to a disturbance of the dynamic balance between excitatory and inhibitory neurotransmitters in the BG. SNc neurons innervate predominantly the striatum, one primary input station of the BG (Fig. 12), a richly interconnected group of brain nuclei playing a key role in the subtle regulation of voluntary and purposive movements (Albin et al., 1989; DeLong, 1990). Experimental studies reveal that the loss of SNc DAergic neurons results in an excessive activity of glutamatergic neurons of the BG, including the corticostriatal afferent pathway (Gubellini et al., 2006; Tseng et al., 2001) and STN efferent neurons (Hirsch et al., 2000), playing a key role in the expression of PD symptoms (Carlsson and Carlsson, 1990; Greenamyre and O'Brien, 1991; Schmidt, 1998). Besides these data, the etiology of the disease remains largely unknown and the available treatments are symptomatic. The discovery of DA deficiency in PD and the therapeutic introduction of L-DOPA, the precursor of DA, revolutionized the treatment of this neurological disease. However, motor fluctuations and dyskinesia complicate L-DOPA treatment in most patients (>90%) within 5–10 years of treatment initiation. These limitations have led to the research and development of alternative therapeutic strategies, including pharmacological treatments bypassing the DA system (for example with anticholinergic drugs) and surgical interventions such as lesioning brain structures and DBS.

The schematic BG organization (Fig. 12A) suggested by Albin and DeLong has been used for many years as a reference for explaining their functioning both in physiological and pathological conditions (Albin et al., 1989; DeLong, 1990). This functional scheme led to the suggestion that the STN could be an interesting lesion target for PD treatment, since it becomes hyperactive in case of DA depletion (DeLong, 1990). Accordingly, although VIM was the first structure targeted, first on the basis of results obtained in parkinsonian monkeys with lesions (Bergman et al., 1990) and then with DBS (Benazzouz et al., 1993), STN has rapidly became the routine target for treating PD on large groups of patients (Pollak et al., 1993), and it still stands as the main target for this surgical therapy, although other brain structures have been considered.

A more recent view of BG organization (Levy et al., 1997) now places the striatum and the STN as the two major input stations of the BG (Fig. 12B). This new model is based on the fact that the former model by DeLong (1990) was unable to explain the lack of decreased activity observed in the GPe in MPTP monkeys or PD patients. Other models of the BG have been proposed in the recent years (Yelnik, 2008), either based on a biologically based computational model of GO/NO GO signal helping in choosing the appropriate solution (Frank et al., 2004, 2007), or insisting on the hyperdirect pathway linking the cortex to the STN as the fastest pathway to clear all the possible actions and enabling the other pathways to select and execute the action (Nambu, 2004). However, it is interesting to note that although this revised

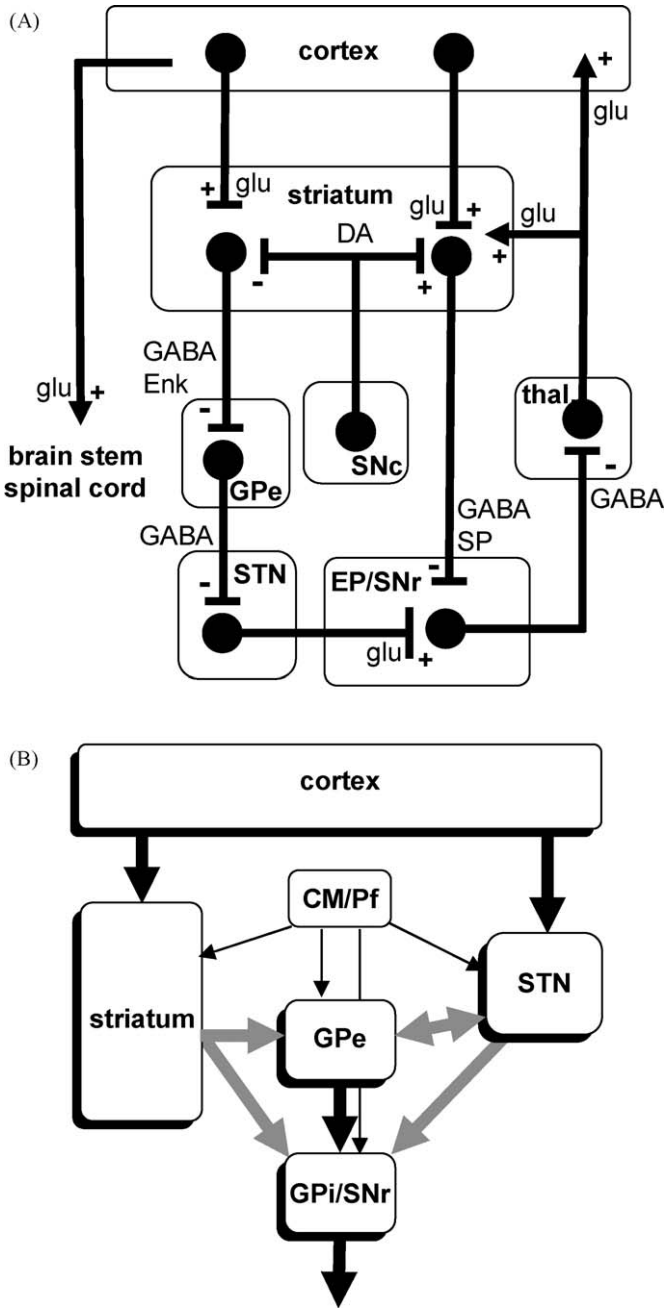

Fig. 12. Scheme of BG circuitry. (A) The "classical" BG circuitry (Albin et al., 1989; DeLong, 1990), with the striatum as the main input station. Note the "direct" striatum-GPi/SNr pathway, and the "indirect" striatum-GPe-STN-GPi/SNr pathway. (B) The more recent BG scheme, where STN has now a status of input station similar to the striatum, i.e., the "hyperdirect" cortex-STN-GPi/SNr pathway (Levy et al., 1997). Abbreviations: CM/Pf, centre median–parafascicular complex of the thalamus; DA, dopamine; GABA, γ-amino butyric acid; Enk, enkephalin; EP, entopeduncular nucleus; glu, glutamate; GPe/i, external/internal part of the globus pallidus; SNc/r; substantia nigra pars compacta/reticulata; SP, substance P; STN, subthalamic nucleus; thal, thalamus.

version of the BG network is more accurate, we still rely on the former one to explain most of the current findings in the literature. Thus, although the clinical advantages of DBS are indisputable, its possible consequences on brain circuitry and function are still under debate, and several other brain structures, besides the STN, have been proposed as possible targets of HFS. To address these issues experimentally, a considerable number of research teams have been studying the effects of DBS in animal models.

3.1. Parkinson's disease and STN stimulation

The rationale for targeting STN in the treatment of PD came not only from BG circuitry, but also from the knowledge that surgical lesion of this structure has a beneficial effect on parkinsonian motor symptoms (Bergman et al., 1990). The first experimental evidence that STN HFS could replace lesion came in 1993 from a study in the monkey by Benazzouz et al. (1993), showing that this technique could alleviate parkinsonian rigidity and bradykinesia, without causing dyskinesia or hemiballism as after STN lesion. In line with this finding, the technique was successfully applied to parkinsonian patients (Pollak et al., 1993). The therapeutic frequency range for bilateral STN HFS that significantly reduces the classical PD motor symptoms (including tremor, bradykinesia and gait impairment) is between 80 and 185 Hz (Bastian et al., 2003; Benabid et al., 1998; Burchiel et al., 1999; Ferrarin et al., 2005; Koller et al., 1999; Kumar et al., 1998; Rizzone et al., 2002; Taha et al., 1999). Targeting the STN by HFS also provides the great bonus consisting of the possibility of reducing DAergic medication: this is a considerable advantage since drug-induced dyskinesia is also reduced, even if indirectly (Kumar et al., 1998; Nutt et al., 2001; Pollak et al., 2002; Russmann et al., 2004). The benefits provided by STN HFS, however, do not exceed those of L-DOPA therapy, measured according to the UPDRS (Jaggi et al., 2004; Pahwa et al., 2005). The improvement of some executive functions has also been reported during STN HFS (Jahanshahi et al., 2000). DBS also presents the advantage of reducing and even eliminating the *off* state time, during which the patient is prostrate with rigidity and bradykinesia. While patients are usually implanted bilaterally, there is now increasing evidence that unilateral STN HFS is also effective in reducing motor symptoms during the *off* medication state (Germano et al., 2004; Kumar et al., 1999b; Limousin et al., 1995; Samii et al., 2007; Slowinski et al., 2007). However, although unilateral stimulation reduces the risks of a bilateral surgery, it can be challenging when this treatment is coupled to L-DOPA, because dyskinesias can be induced asymmetrically by HFS itself and/or by L-DOPA that acts bilaterally. Thus, bilateral stimulation is still preferred to unilateral.

During the last decade, several studies performed in parkinsonian patients during DBS electrode implantation have revealed, by measuring local field potential, that BG–cortical loops have an oscillatory and synchronized activity between 8 Hz and 30 Hz, the above-mentioned β frequency band. Interestingly, such synchronization is disrupted by L-DOPA treatment and STN HFS, suggesting that: (i) β oscillations of BG-cortical loops might be related to PD motor impairment, and (ii) that one action mechanism of DBS, as well as DAergic medication, could be the disruption of this synchronization (Brown and Eusebio, 2008; Garcia et al., 2005a; Hammond et al., 2007; McIntyre et al., 2004b).

Beside the above-described positive effects on motor performance, however, STN stimulation can have undesired side-effects and drawbacks. In PD patients, STN HFS can induce *per se* abnormal involuntary movement (dyskinesia) at high voltage (Limousin et al., 1996). In general, the appearance of STN HFS-induced dyskinesia during surgery or the initial postoperative programming period is considered as a favorable sign predicting beneficial postoperative outcome (Houeto et al., 2003). Usually, the dyskinesia-inducing effect progressively declines and can be managed by adjusting dopaminergic medication and stimulation parameters (Krack et al., 2002): the antiparkinsonian benefit provided by the stimulation reduces dopaminergic medication requirement, and the decrease in L-DOPA reduces L-DOPA-induced dyskinesia and allows, in parallel, keeping stimulation amplitude low. Thus, as mentioned above, the relief of dyskinesia by STN HFS is thought to be indirect, due to the postoperative reduction of dopaminergic medication (Follett, 2004; Krack et al., 2002;

Russmann et al., 2004). The postoperative management of patients with STN HFS is complicated by persistent dyskinesia in rare cases, despite maximal reduction of dopaminergic medication and antidyskinetic drug therapy (such as amantadine). A recent study reports that, in those patients, additional stimulation of a proximal contact located within pallidofugal fibers may lead to a significant reduction of dyskinesia associated with STN HFS (Herzog et al., 2007b).

It is important to note that, although DBS is currently the preferred surgical strategy for PD, lesions are still an alternative strategy used for some patients. Thalamotomies and pallidotomies have been used with a certain success but also some side-effects (Okun and Vitek, 2004). STN lesions are also performed in some cases. They have been performed unilaterally and showed beneficial effects on motor scores (Gill and Heywood, 1997), but could also induce intractable hemiballism (Patel et al., 2003; Su et al., 2003). It seems that bilateral lesions prevent this side-effect and have beneficial effects in PD patients that are somewhat equivalent to STN DBS (Alvarez et al., 2005; Su et al., 2002).

Although STN represents the main target for the treatment of PD by DBS, other brain structures have been also successfully targeted, such as GPi, VIM and, more recently, PPN and centre median–parafascicular (CM/Pf) complex of the thalamus (see Section 3.3).

3.2. STN stimulation for Parkinson's disease: from motor to complex behavior

3.2.1. Motor behavior

As mentioned above, before applying DBS, it was more common to test the effects of lesions in animal models of PD. From an historical point of view, and also because DBS studies carried out in animals frequently refer and compare to lesion studies, the effects of lesions will be presented briefly as well in this section.

3.2.1.1. STN lesion. Let us consider the effects of STN lesion in the intact monkey: it was first reported that it induced a characteristic hyperkinetic syndrome called "ballism" or "hemiballism" (Carpenter et al., 1950; Carpenter, 1955; Whittier and Mettler, 1949). The first paper showing antiparkinsonian effects of STN lesions in MPTP monkey was published by Bergman et al. (1990). It was based on a serious impairment of gross motor behavior induced by MPTP, which could be alleviated by STN lesions. This pioneer study was further confirmed by the study by Aziz et al. (1991). In line with these reports, it was also shown that subthalamotomy performed in parkinsonian monkeys had a beneficial effect on certain motor deficits, but could also be detrimental by inducing hyperkinetic movements, hemiballism or by failing in correcting deficits in skilled movements (Guridi et al., 1994, 1996; Henderson et al., 1998; Wichmann et al., 1994). Akinesia and bradykinesia were strongly ameliorated by discrete inactivation with muscimol of the lateral part of the sensorimotor territory in STN (Baron et al., 2002).

In intact rats, unilateral lesions of the STN only produce transient hyperkinetic movements of the contralateral paw (Kafetzopoulos and Papadopoulos, 1983). When the lesion is bilateral, this behavioral effect was rarely described. Only a trend to hyperlocomotion has been reported, as well as premature responses in reaction time procedures (Baunez et al., 1995a). In rat models of PD, it was first shown that lesions of the STN alleviated the cataleptic state induced by a high dose of haloperidol (Zadow and Schmidt, 1994). When performed unilaterally, STN lesions can reduce circling behavior induced by either a D2 agonist or apomorphine, and alleviate postural asymmetry and improve limb-use asymmetry in hemiparkinsonian rats (Anderson et al., 1992; Blandini et al., 1997; Burbaud et al., 1995; Centonze et al., 2005; Phillips et al., 1998). In order to measure the effects of bilateral STN lesions in a rat model of early parkinsonism, we have tested the effects of these lesions in parkinsonian rats performing a task allowing a subtle measure of simple reaction time (RT) task (Fig. 13). Parkinsonian patients suffering from akinesia are known to exhibit increased RT in these tasks (Bloxham et al., 1984; Gauntlett-Gilbert and Brown, 1998; Jahanshahi et al., 1992). As shown in Fig. 13, bilateral lesions of DA terminals in the dorsal striatum increased the number of delayed responses as well as the mean RT for correct responses, which is typical of an akinetic-like

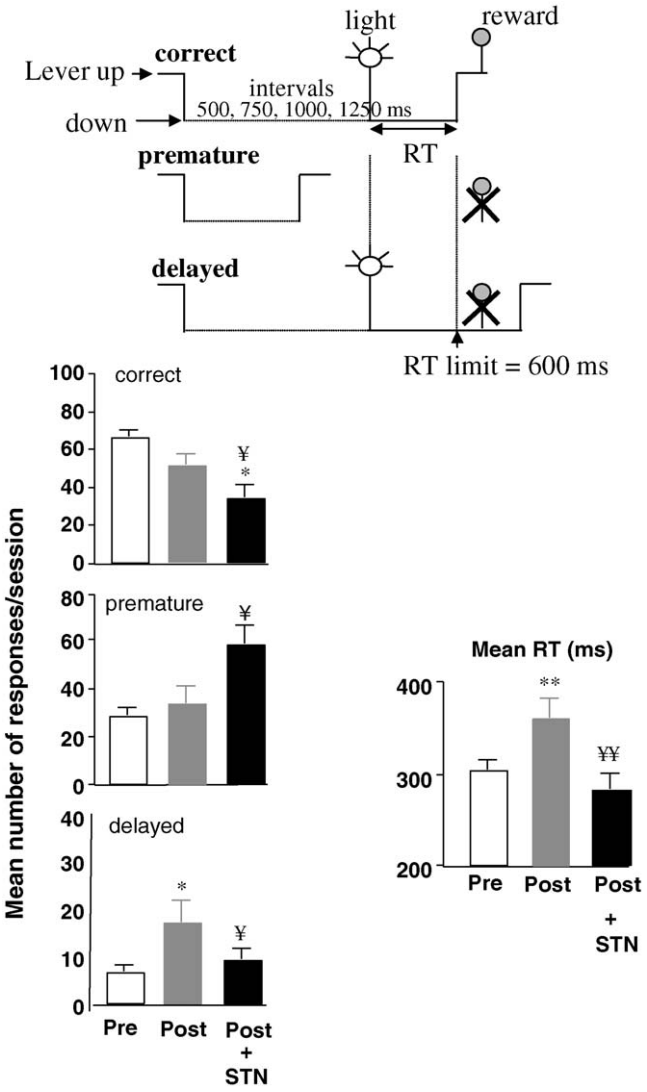

Fig. 13. Simple reaction time task in the rat and effects of STN lesions in a rat model of PD. The simple reaction time (RT) task used in the rat (upper panel). The rat is trained to press a lever and sustain its paw on it until the occurrence of a visual stimulus (a light), which happens randomly after 500, 750, 1000 or 1250 ms. At the presentation of the light, the rat has to release the lever within 600 ms (i.e., RT) to get a food pellet as a reward. Three types of responses are possible: (1) correct, (2) premature, when the rat withdraws its paw from the lever before the presentation of the light, and (3) delayed, when the rat releases the lever after the presentation of the light, but with a reaction time exceeding 600 ms. The four graphs show the effects of the dopaminergic depletion of the dorsal striatum (Post) followed by an excitotoxic lesion of the STN (Post + STN), compared to control (Pre). DA lesion induced an akinetic-like deficit characterized by an increased number of delayed responses and an overall increased RT for correct responses. Bilateral STN lesion alleviated these two major deficits, but further affected the performance in terms of correct responses because of a dramatic premature-responding deficit. *, **: significant difference from pre-operative performance, ¥, ¥¥: significant difference from postoperative performance (6-OHDA lesion effect), $p < 0.05$ and 0.01 respectively [see Baunez et al., 1995b].

pattern of performance. Consecutive bilateral lesions of the STN alleviate this akinetic-like deficit, but the rats maintain a poor level of performance in the task due to the appearance of a premature-responding deficit (Baunez et al., 1995a). Although this study confirmed the beneficial effect of STN inactivation on motor disabilities in PD, it also revealed for the first time possible side-effects that might be related to the involvement of STN in non-motor behavior. These results were confirmed later by studies carried out with unilateral lesions showing beneficial effects with side-effects, such as premature responses or a paw reaching deficit (Henderson et al., 1999; Phillips and Brown, 1999).

3.2.1.2. STN HFS. As mentioned above, Benazzouz et al. (1993) were the first to show that unilateral STN HFS, applied in monkeys rendered hemiparkinsonian with MPTP, alleviated the muscular rigidity observed in the contralateral forelimb. This pioneer work was actually at the origin of the idea to apply STN HFS in PD patients. In the intact monkey, STN HFS elicits dyskinesias contralateral to the stimulated STN that resembles hemiballism induced by STN lesion (Beurrier et al., 1997). In contrast to what was described after STN lesions, STN HFS does not seem to induce hyperkinetic movements when applied to MPTP monkeys and when compared to L-DOPA effects (Benazzouz et al., 1996).

The first behavioral study published on STN HFS in freely moving rats used unilateral HFS as well as unilateral DA depletion in the SNc. The study assessed both basic motor tasks such as haloperidol-induced catalepsy and apomorphine-induced circling behavior, as well as choice reaction time task (Darbaky et al., 2003). In this study, we have shown that both a cataleptic state induced by haloperidol and circling behavior induced by apomorphine could be alleviated by unilateral STN HFS applied for 90 min. However, in the choice RT task, only a few animals remained able to perform the task after DA depletion (Fig. 14A) and STN HFS was unable to help those that were not able to work on the task. This was in contrast to the spectacular effect of STN HFS in PD patients, since the stimulation applied here in the rat could not overcome the profound deficit preventing the animals from performing the task. Interestingly, however, for the animals able to work on the task, STN HFS alleviated the deficit expressed as a decreased ability of hemiparkinsonian rats to initiate a response towards the side contralateral to DA lesion (Fig. 14B) (Darbaky et al., 2003). The conclusion of that study was that STN HFS could be beneficial for the treatment of motor deficit, but non-efficient when the cognitive load was higher, leading to further cognitive studies developed in the next part. Later the same year, Chang et al. (2003), even applying very short stimulations, showed that STN HFS had a beneficial effect on treadmill walking in parkinsonian rats, while Shi et al. (2004) have shown a reduced asymmetry when STN HFS was applied in hemiparkinsonian rats. We have shown (Gubellini et al., 2006) recently that continuous application of STN HFS for several days could progressively restore the spontaneous use of the contralateral paw that was impaired after 6-OHDA lesion, but was not efficient in alleviating L-DOPA-induced dyskinesia in hemiparkinsonian rats, in line with the lesion study published by Marin et al. (2004).

Interestingly, STN HFS applied in the rat can produce sequentially, with gradual increased intensity, the different subtypes of abnormal involuntary movements induced by chronic L-DOPA, with the following sequence: orofacial dyskinetic movements, dyskinetic movements of the contralateral forelimb, strong contralateral bias in the head position and, finally, contralateral rotation. This dyskinesia-inducing effect is observed both in naïve rats and rats with DA denervation, previously treated with L-DOPA or not (Oueslati et al., 2007), and is thus not strictly dependent on DA tone. However, the threshold for induction of dyskinesias is increased in parkinsonian vs. naïve rats and further increased in those previously treated with L-DOPA that showed dyskinesias, reinforcing the view of a modulatory

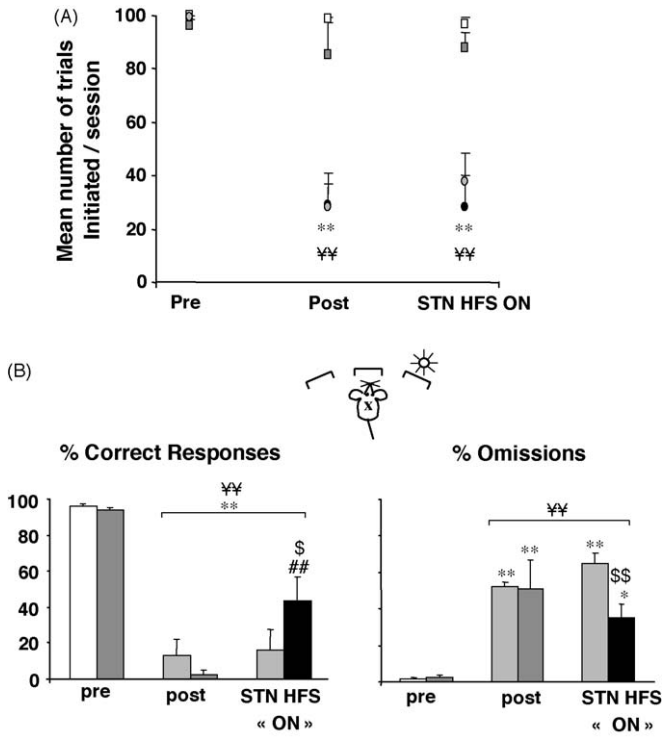

Fig. 14. Performance in a choice reaction time task after unilateral 6-OHDA infusion in the SNc and unilateral STN HFS. (A) Number of trials initiated during the various phases of the experiment before surgery (Pre), after 6-OHDA lesion with stimulation OFF (Post), and after 6-OHDA lesion with the stimulation ON (STN HFS ON) for the 4 groups: sham (empty squares), sham HFS (grey squares), 6-OHDA (grey circles) and 6-OHDA-HFS (black circles). (B) Performance of the animals of the two groups subjected to 6-OHDA lesion [6-OHDA (white and light grey bars) and 6-OHDA-HFS (dark grey and black bars)] still able to work after DA depletion in terms of accuracy of responses (% correct responses) and omissions towards the contralateral of the DA lesion. *, **: significant difference from pre-operative performance, ¥, ¥¥: significant difference from sham-control group's performance (not illustrated here), $$: significant difference from 6-OHDA non-stimulated group, $p < 0.05$ and 0.01 respectively [see Darbaky et al., 2003].

role of DA on the responsiveness to STN HFS. For example, it has been shown that the STN stimulation-induced contralateral circling is differentially modulated through DA D1 and D2 receptors, and that forelimb dyskinesia is linked to an increase in glutamate levels in the SNr (Bergmann et al., 2004), whereas the anti-akinetic action of the STN stimulation at lower intensity is linked to increased nigral GABA levels (Boulet et al., 2006). These observations also suggest that PD patients with prior L-DOPA treatment would be less susceptible to dyskinesias induced by STN HFS than untreated ones. Moreover, it is to note that dyskinesia produced by STN HFS is transient. For instance, when maintaining a stimulation intensity initially producing forelimb dyskinesia, the dyskinesiogenic effect rapidly disappears and further increase in the intensity is required to re-induce this response (Boulet et al., 2006; Oueslati et al., 2007). Thus, not only is dyskinesia not maintained, but the threshold for its induction progressively increases with prolonged HFS. For example, after 2 h of HFS at low intensity, the threshold of forelimb dyskinesia induction is substantially increased compared with that determined within the first minutes of stimulation, and in some cases it cannot be reached anymore. These observations indicate that rapid adaptive mechanisms counterbalance such side-effects of STN HFS. When applied in intact rats, unilateral STN HFS induces contralateral circling behavior that can be reduced by DAergic antagonists (Bergmann et al., 2004).

The first study testing the effects of bilateral STN HFS was carried out in intact rats and was applied at various parameters in rats performing a RT task. STN HFS in that study decreased the

premature responses depending on the parameters applied (Desbonnet et al., 2004). The same group confirmed such effect on premature responses at different parameters than those alleviating RT deficits in parkinsonian rats (Temel et al., 2005) and also showed improvement on locomotion (Vlamings et al., 2007). On many aspects of motor behavior, STN HFS, although not applied always in the same manner (monopolar, bipolar, unilateral, bilateral, individual adjusted parameters or not, duration of the stimulation, schedule of the ON/OFF periods), the consensus seems to show a beneficial effect on motor deficits induced by DA lesion. However, the question of a possible detrimental, or at least a lack of, effect on cognitive processes was raised and needed to be further investigated. The animal experimental data (Darbaky et al., 2003; Temel et al., 2005) seem thus to confirm the non-systematic correlation between motor and cognitive effects of STN HFS, as reported in human patients (Perriol et al., 2006).

3.2.2. Cognitive behavior

When considering the connectivity of the BG described as five parallel loops (motor, oculo-motor, prefrontal–dorsolateral, lateral orbitofrontal and limbic loops corresponding to the connectivity of a specific cortical territory to a corresponding territory of each structure of the BG), the STN belongs to each loop and should not therefore be considered only as contributing to motor behavior (Alexander et al., 1986). As illustrated in Fig. 15, the STN receives direct connections from the prefrontal cortex. Therefore, manipulation of the STN should have consequences on frontal functions, as much as it has on motor processes. The STN is also connected more or less directly with structures such as the NAc and the ventral pallidum, well-known for their involvement in motivational processes. These anatomical considerations led us to investigate the involvement of the STN in non-motor behavior. However, only a limited number of groups study the effects of STN HFS in animals and none have published yet any study investigating its possible effects on cognitive processes in the monkey. The number of investigations focusing on cognitive processes in human patients has increased in recent years and might explain why there is little interest for these studies applied to monkeys. Most of the studies reported here were thus carried out in rodents and mainly with lesions of the STN rather than DBS.

3.2.2.1. STN lesion. It is interesting to note first that assessment of STN lesions in PD patients on cognitive functions revealed slight adverse cognitive effects. These changes are reported to affect verbal learning and memory (Patel et al., 2003). In animals, there are only a few studies dedicated to the involvement of STN in learning and memory processes. Recently, it has been shown that STN lesion does not affect seriously learning processes, but can affect working memory (El Massioui et al., 2007), in line with a former study showing working memory deficits in a choice RT task (Baunez et al., 2001), but these studies were not carried out in PD models. In a study using a simple RT task (Baunez et al., 1995b), we suggested that premature responses could reflect an attentional impairment. We used the 5-choice serial RT task (Fig. 16) to study the effects of STN lesions alone and then of STN lesions combined with a bilateral DA depletion in the dorsal striatum. We showed that bilateral excitotoxic STN lesion induced multiple independent deficits in the task such as impaired accuracy, suggestive of an attentional deficit, increased level of premature responses, suggestive of increased impulsivity, and increased level of perseverative responses towards the response locations and the magazine where the animals collect the food reward, which is suggestive of a deficit in response control and increased level of motivation for the reward (Figs. 17 and 18) (Baunez and Robbins, 1997). These results were the first to highlight the involvement of

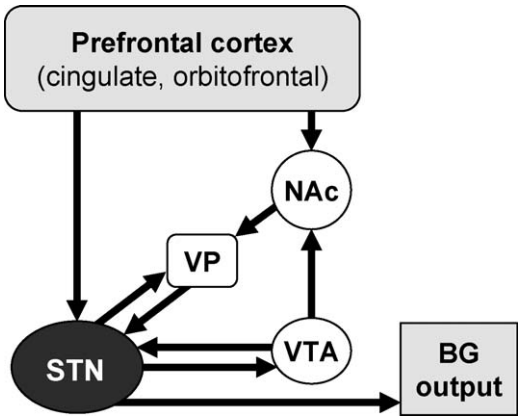

Fig. 15. The STN in the limbic loop. Besides its connections with the basal ganglia (BG), the STN receives direct inputs from the prefrontal cortex, and it is indirectly connected with the nucleus accumbens (NAc) via the ventral pallidum (VP). It also receives inputs from the DA nuclei, including the ventral tegmental area (VTA) and the substantia nigra pars compacta (not represented).

STN in cognitive functions. They were also replicated after the blockade of $GABA_A$ receptors into the STN with muscimol (Baunez and Robbins, 1999b). When lesioning DA inputs to the dorsal striatum, we did not affect dramatically the level of performance in the attentional task, although there was a slight impairment in visual attention. However, most of the deficits (omissions and increased latencies) were more motor-related (Baunez and Robbins, 1999a). Interestingly, when combining striatal DA lesion with STN lesions, the performance was further impaired. One of the most striking effects was observed on perseverative responses towards the food magazine, suggesting an increased level of motivation for the reward (Baunez and Robbins, 1999a). In a study using a disconnection between the medial prefrontal cortex and the STN (lesioning the prefrontal cortex on one side and the STN on

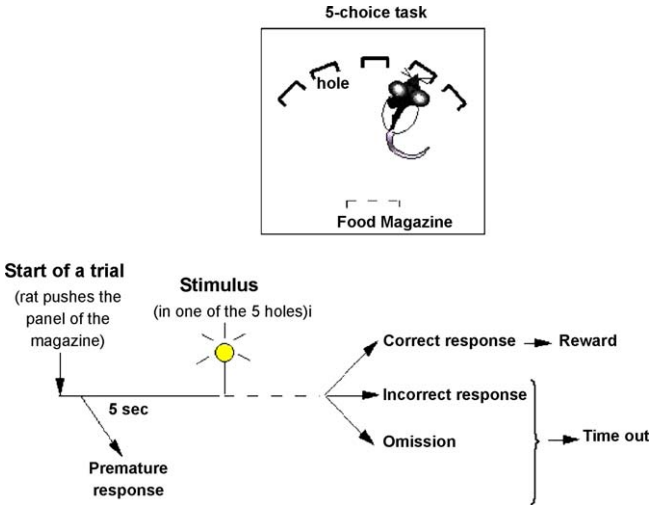

Fig. 16. The 5-choice serial reaction time task (5-CSRTT). Each rat was trained to initiate a trial by a nose-poke in the food-magazine. After a 5 sec delay, a brief light (500 ms) was presented in one of the five holes. The rat had to detect and respond by a nose-poke in the illuminated hole within 5 s to obtain a reward, collect it in the magazine and then start the next trial. In case of an early response in a hole before the presentation of the light, the response was recorded as a premature response and punished by a time-out (extinction of the house-light). The same punishment occurred if the rat responded in the wrong hole (incorrect response) or did not respond within 5 s (omission). After the first response had been given, additional nose-pokes in the various holes were recorded as "perseverative responses". Detection of the rat's nose in the food-magazine other than the first one after reward delivery were recorded as "perseverative panel pushes", characterizing inappropriate visits to the food-magazine.

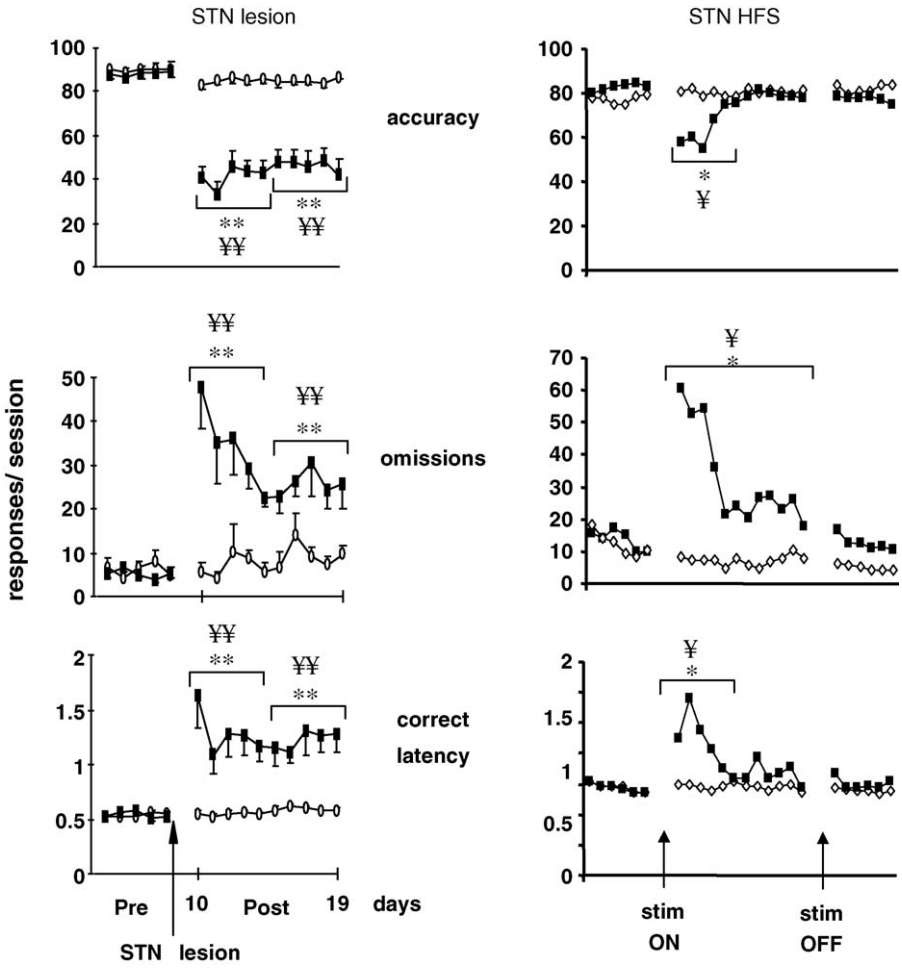

Fig. 17. Effects of bilateral STN lesion and STN HFS in the 5-choice serial reaction time task (5-CSRTT). The performance in the 5-CSRTT is illustrated here for accuracy of performance (% of correct responses), number of omissions and mean latency to make correct responses (correct latency). STN lesioned animals (filled squares) are compared to sham-operated (empty circles) in the left panel. Animals subjected to bilateral STN HFS and their control (filled squares and empty diamonds respectively) are shown in the right panel. *, **: significant difference from pre-operative performance, ¥, ¥¥: significant difference from control group's performance, $p < 0.05$ and 0.01 respectively (Baunez et al., 2007; used with permission from Baunez and Robbins, 1997).

the other side), we have given the first evidence of a functional role of the hyperdirect pathway linking the cortex to the STN in the attentional and perseverative deficits observed in the attentional task (Chudasama et al., 2003). Interestingly, the paper from Patel et al. (2003) on unilateral lesion of STN in PD patients also report attentional deficits in some cases.

3.2.2.2. STN HFS. We previously developed the idea that a premature response in a RT task may reflect some cognitive deficit that relates to either an attentional deficit or a deficit in inhibition control. DAergic depletion of the dorsal striatum can sometimes induce an increased number of premature responses (Turle-Lorenzo et al., 2006). Temel et al. (2005) also reported this type of deficit in parkinsonian rats performing a choice RT task, together with increased RT and movement time (MT). Interestingly, they showed that bilateral STN HFS could alleviate the premature-responding deficit at a lower current intensity (3 μA) than that reducing RT and MT (30 μA). As mentioned above, this study provided the evidence that cognitive and motor deficits may require a different threshold of HFS intensity to be treated. In intact and parkinsonian rats, we tested the effects of bilateral STN HFS and could therefore compare them to those induced by bilateral excitotoxic STN lesions in the visual attentional task described above. As illustrated for the intact animals in Figs. 17 and 18, the effects of STN HFS were slightly different from those induced by STN lesions. Accuracy of performance and latency to make a correct response were only transiently affected, while no effect on premature responses could be observed. Interestingly, perseverative responses on both response location and reward magazine were found, in line with the lesion study (Baunez et al., 2007). In parkinsonian rats, the subtle deficits recorded in the 5-choice RT task were not further deteriorated by bilateral STN HFS, nor alleviated. The most striking effect was observed on the perseverative responses recorded in the food-magazine, suggesting that STN HFS increases motivation for the food reward (Baunez et al., 2007), which is somehow in line with some non-motor side-effects of STN HFS applied in PD patients that produce weight gain (Barichella et al., 2003). In parkinsonian patients, STN HFS stimulation can reduce working memory and impair cognitive motor control (Hershey et al., 2004) as well as conditional associative learning (Jahanshahi et al., 2000). Finally, as mentioned before, in some cases STN HFS can produce psychiatric effects, including cognitive alterations and hallucinations (Diederich et al., 2000), manic episodes (Herzog et al., 2003), mood disorders (Berney et al., 2002), and impulsive behavior (Kopell and Greenberg, 2008; Perlmutter and Mink, 2006).

3.2.3. Motivational behavior

As suggested by our study in the attentional task, STN seems to play a role in motivational processes (see also Section 5.2).

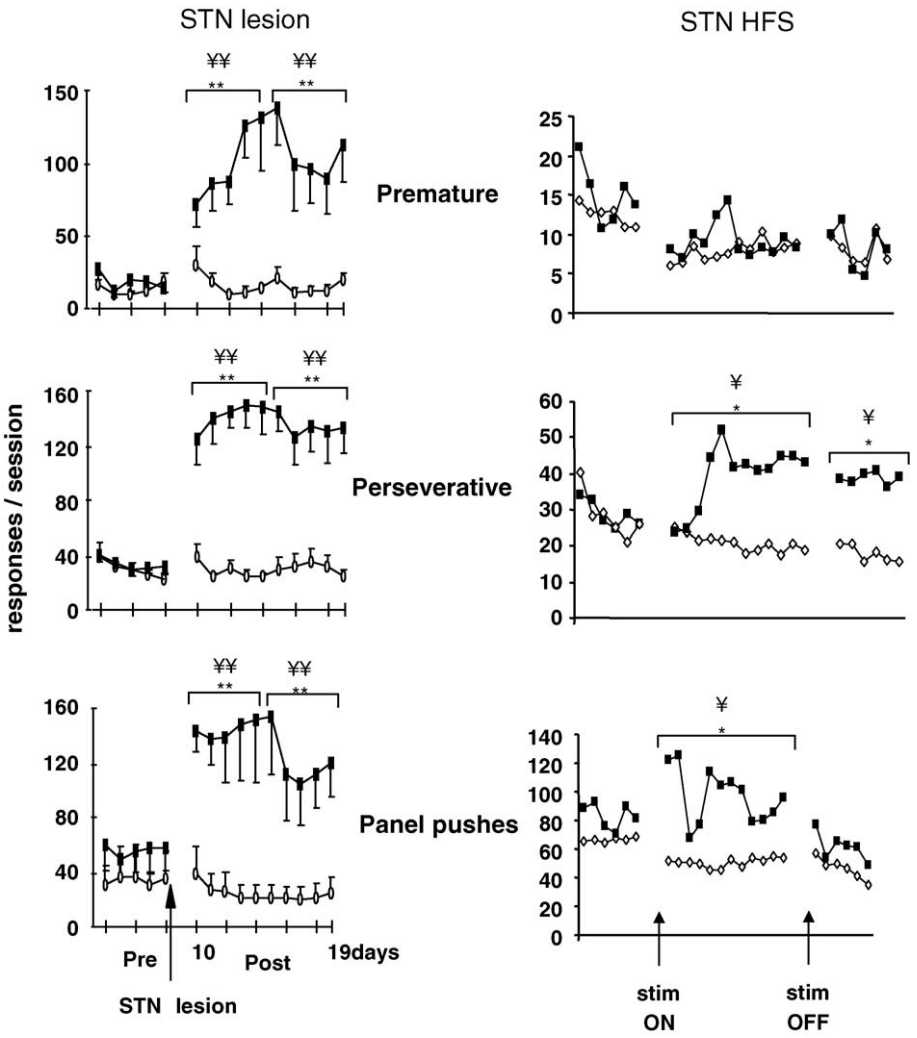

Fig. 18. Effects of bilateral lesion and STN HFS in the 5-choice serial reaction time task (5-CSRTT). The performance in the 5-CSRTT is illustrated here for premature responses, perseverative responses and perseverative responses into the food magazine (panel pushes) in the sham-operated and STN lesioned animals (empty circles and filled squares respectively; left panel) and in the animals subjected to bilateral STN HFS and their control (filled squares and empty diamonds respectively, right panel). *, **: significant difference from pre-operative performance, ¥, ¥¥: significant difference from control group's performance, $p < 0.05$ and 0.01 respectively (Baunez et al., 2007; used with permission from Baunez and Robbins, 1997).

However, most of the studies carried out in animals to address this issue did not use animal models of PD. In PD patients, clinicians often report that STN DBS can induce in some patients craving for sweet food. However, no published report of such behavior is available to date. It is well known that STN stimulation induces weight gain in PD patients (Barichella et al., 2003; Deuschl et al., 2006; Macia et al., 2004; Montaurier et al., 2007), but this is most frequently discussed in terms of metabolism and activity and not really discussed in terms of increased motivation. Interestingly, STN DBS applied in PD patients suffering from DA dysregulation syndrome abolished the addiction for the dopaminergic treatment (Witjas et al., 2005).

3.2.4. Conclusions

When investigating motor behavior, numerous studies carried out in animal models have provided pioneering data supporting the hypothesis that STN could represent an interesting target for the treatment of PD. They almost all confirmed the beneficial effects on motor behavior of such a surgical strategy in animals. In general, there is a poor investigation of behavioral consequences of STN DBS carried out in monkeys, possibly due to the fact that numerous clinical reports are published every month and might thus reduce the interest in testing behavioral effects in non-human primates of this surgical strategy. Most of the available studies using DBS in monkeys aimed at understanding the cellular mechanisms of DBS. It would be however of great interest to also study the effects on behavior to better understand the functional role of STN in the BG, especially regarding non-motor behavior. Thus, when it comes to cognitive and motivational processes in animal models, only rat data are available. Overall, these studies highlighted the integrative function of the STN, placing it at the interface between motivation and action. These studies led to a more cautious attitude towards the selection criteria for surgery. Indeed, with the development of interest in cognitive and psychiatric consequences of STN HFS, the psychiatric examination of PD patients has been taken more seriously in order to anticipate and avoid possible side-effects of STN HFS. There were often clinical observations of PD patients with STN DBS in parallel to these experimental findings, but further studies in monkeys would be important to perform, especially because they could allow specific investigation of the sub-territories within the STN (limbic, associative and motor areas), which is impossible in the rat given the size of the STN in this animal.

In conclusion, a better knowledge of the possible consequences of STN (or GPi) inactivation in animals on various types of behavior involving motor, cognitive and motivational processes was

important for the treatment of PD patients and led to a more cautious attitude towards the selection criteria for surgery. Indeed, with the development of the interest in cognitive and psychiatric consequences of STN HFS, the psychiatric examination of the patients has been taken more seriously in order to anticipate and avoid possible side-effects of STN HFS.

3.3. Stimulation of other brain structures for Parkinson's disease

3.3.1. Zona incerta and prelemniscal radiation

Several reports have highlighted the value of DBS of the posterior subthalamic white matter, including the zona incerta (ZI) and the prelemniscal radiation, as a reliable therapeutic approach for the treatment of tremor-dominant PD. The prelemniscal radiation is a bundle of fibers in the posterior subthalamic area that can be visualized easily on ventriculograms. This area, considered as part of a reticulothalamic system involved in the control of muscle tone and the manifestation of tremor, as well as in the process of selective attention, has long been proposed as a lesion target for the relief of tremor (Velasco et al., 1976). Unilateral DBS of the prelemniscal radiation has also been applied for the treatment of tremor and rigidity in PD patients predominantly affected in one side (Velasco et al., 2001a), and recently noted that bilateral DBS alleviates the triad of motor symptoms in patients with advanced PD (Carrillo-Ruiz et al., 2008). In addition, this target seems suitable for relief of intractable dyskinesias (Herzog et al., 2007b). HFS of the ZI has been reported by Plaha et al. (2006) to be superior to STN HFS for improving contralateral parkinsonism in PD patients. They measured the contralateral UPDRS motor score on tremor, bradykinesia and rigidity, which were all improved by stimulating caudal ZI more than STN, suggesting that this structure may be a valuable alternative target for the treatment of tremor and PD with DBS (Plaha et al., 2008). It is however puzzling that for most studies carried out in rats, when lesions or DBS affect the ZI instead of the STN, the effects are different and less efficient, questioning the role of the ZI or maybe the current diffusion effect in the above reports.

3.3.2. GPi

The GPi has been one of the first targets to be investigated, together with the thalamus, for movement disorders (Bejjani et al., 1997; Siegfried and Lippitz, 1994a, 1994b). Efficacy of GPi DBS has been shown to depend on the modality and site of stimulation (Peppe et al., 2001), and has been reported having questionable effects on extrapyramidal signs and worsening conditional associative learning. However, GPi DBS has also proven to significantly improve a wide range of PD symptoms (Anderson et al., 2005), even up to 3–4 years after surgery (Rodriguez-Oroz et al., 2005). Chronic HFS of the GPi, contrary to STN, does not allow reducing L-DOPA treatment, but it seems to have a direct antidyskinetic action, so that it remains a suitable option for patients with severe dyskinesia. Indeed, GPi stimulation decreases dyskinesia in most patients, though the effect on *off* motor symptoms is variable, whereas STN stimulation, which greatly decreases *off* motor symptoms and motor fluctuations, seems to reduce dyskinesias by allowing a reduction of L-DOPA dosage, as mentioned above (Follett, 2004; Krack et al., 1998; Limousin-Dowsey et al., 1999). In this context, it is to note that experimental evidence for differential mechanisms of action between HFS of the GPi and the STN has been provided, which could help to explain differences in clinical outcome. For instance, neurochemical investigations in the rat have shown that HFS of EP (the rodent homologous of GPi) has no effect on striatal DA transmission (Meissner et al., 2004), whereas STN HFS has been reported to increase striatal DA release and metabolism (Bruet et al., 2001; Lee et al., 2006; Meissner et al., 2002, 2003). Whether EP HFS interferes differently from STN with the neurochemical and cellular effects of L-DOPA is thus an important issue to be addressed. A study on rat EP slices supports an inhibitory effect of HFS, by showing that it induces an increase of extracellular potassium, which decreased EP neuronal activity by activating an ion conductance resulting in membrane depolarization, independent of synaptic involvement (Shin et al., 2007). On the other hand, a recent study performed on MPTP monkeys stimulated in the GPi reported only slight reductions of GPi neuronal firing, paralleled by improvement of rigidity and posture. The effects of GPi HFS included a combination of stimulation-driven firing, phasic facilitations and firing suppression; only a minority of cells showed AP suppression. However, GPi HFS suppressed synchronized oscillations in both the GPi and GPe (McCairn and Turner, 2009). These findings thus support the hypothesis that GPi HFS could reduce PD motor troubles by suppressing the low-frequency oscillatory activity associated with PD.

3.3.3. Thalamus

Thalamic DBS targeting VIM was the first approach developed for the treatment of PD and has proven to be a very effective treatment for tremor (Benabid et al., 1987, 1993). Its limitation is the slight or lack of effect on other motor symptoms. Moreover, in some cases VIM DBS loses its efficacy after a few years and parkinsonian patients under thalamic stimulation still need dopaminergic medication (Benabid et al., 1996; Kumar et al., 2003; Putzke et al., 2003). However, VIM DBS remains an option for patients with severe tremor, when STN DBS is not advised. The centre median–parafascicular complex of the thalamus (CM/Pf), which represents an important input and output system of the BG, has been proposed as a potential target for movement disorders, including tremor and dyskinesias. On the one hand, there is evidence that CM/Pf DBS, used in the treatment of chronic intractable pain, can efficiently relieve both the pain and the associated or additional motor disorders (Andy, 1980; Krauss et al., 2002). On the other hand, retrospective analysis of the different results of two studies performing thalamic DBS for treating parkinsonian tremor suggested that improvement of L-DOPA-induced dyskinesia in addition to tremor was related to the placement of the electrode closer to CM/Pf than VIM (Caparros-Lefebvre et al., 1999). A recent clinical study, however, confirmed the efficiency of CM/Pf DBS for reducing tremor in patients with advanced PD (Peppe et al., 2008). Interest for this target is supported by clinical and experimental data showing loss of CM/Pf neurons in PD state and reactive changes in the activity of the remaining neurons, which are possibly involved in the pathophysiology of PD (Aymerich et al., 2006; Bacci et al., 2004b; Henderson et al., 2000a, 2000b; Lanciego et al., 2009; Orieux et al., 2000). Data from our group showed that HFS of CM/Pf efficiently alleviates akinesia in a rat model of PD, suggesting that this action may involve BG subcircuits different from those underlying the anti-akinetic effect of STN DBS (Kerkerian-Le Goff et al., 2009). The overall data available on CM/Pf DBS suggest that this treatment deserves further attention in the context of movement disorders.

3.3.4. Pedunculopontine nucleus

Gait disorders and postural instability are disabling symptoms of idiopathic PD and, in late stages of the disease, they can be resistant to both pharmacological and surgical therapies. Although the anatomical and physiological substrates for these motor troubles are poorly understood, several lines of evidence suggest a possible role of the pedunculopontine nucleus (PPN), a component of the mesencephalic locomotor region (Pahapill and Lozano, 2000). PPN receives inhibitory GABAergic afferents from GPi/SNr neurons and projects to thalamus, BG, cerebral cortex and spinal cord. Electrical or drug-induced activation of PPN can elicit

locomotor activity in experimental animals. Inversely, experimental PPN lesions in normal monkeys result in akinesia. In PD state, overactive GABA outflow from BG should depress PPN activity. Furthermore, PD patients have significant loss of PPN neurons. These data thus suggest that the degeneration/dysfunction of PPN neurons may be important in the pathophysiology of locomotor and postural disturbances of PD. Further evidence for a relationship between PPN activity and postural stability has been provided by the recent observation of a correlation between the improvement of postural reflexes in PD patients treated by STN DBS and rCBF changes in the PPN (Karimi et al., 2008).

Jenkinson et al. (2004) described the effects of PPN DBS in the monkey, before and after induction of PD by MPTP treatment. They showed that motor activity is increased by LFS (5 Hz) while it is decreased by HFS (100 Hz) in control conditions. LFS also significantly restored activity in parkinsonian state, which was interpreted as consistent with the hypothesis of PPN hypoactivity in severe forms of PD. In a following study, this group further provided evidence for an additive beneficial effect of PPN DBS and L-DOPA, suggesting that these two treatments have independent sites of action (Jenkinson et al., 2006). Since 2005, several reports have supported the therapeutic potential of PPN LFS in PD patients. The investigation by Mazzone et al. (2005), mainly focused on electrophysiological properties of PPN neurons, showed that DBS at 10 Hz induced a subjective feeling of "well being", which was time-locked with a modest improvement in motor function, whereas at 80 Hz it had no discernable effect. Plaha and Gill (2005) reported for the first time that PPN DBS improved gait dysfunction and postural instability, along with bradykinesia and rigidity, with the best responses at 20–25 Hz. More recently, Stefani and colleagues noted that PPN DBS alone has modest and not sustained effect on hypokinetic signs and, when associated with STN DBS, does not provide additional benefit in the medication *off* state but it strikingly ameliorates UPDRS score during the *on* time. They suggested that PPN might not be a fully alternative target, but rather to be considered in combination with STN DBS for improving gait and optimizing the DA-mediated *on* state (Stefani et al., 2007). It is to note, however, that the structure that was stimulated for this work has been questioned (Yelnik, 2007; Zrinzo et al., 2007). Although preliminary evidences are encouraging, there is a clear need of additional studies to establish the role and optimal conditions of PPN DBS for PD treatment.

The fact that DBS of PPN typically provides benefits at low frequency, whereas therapeutic action is obtained at high frequency for the other targets, raises questions as to the pathological activity of PPN and the mechanism of action of its stimulation. PPN is commonly considered as hypoactive in PD due to increased inhibitory BG outflow, and the benefits provided by PPN LFS can be thought to result from direct activation of this nucleus. However, electrophysiological support for the hypothesis of PPN hypoactivity in PD state is poor and metabolic evidences rather suggest an overactivity of PPN neurons projecting to STN in rat PD model (Orieux et al., 2000). Local field potential recordings have recently shown synchronization of low-frequency activity in the PPN of a PD patient, which increased after treatment with DA; it has been suggested that PPN LFS might mimic such effect (Androulidakis et al., 2008). Regarding the neural substrates of the benefits provided by PPN DBS, a recent study investigated its effect on spinal reflex excitability in patients, by utilizing the soleus-Hoffman reflex threshold (Pierantozzi et al., 2008). It is shown that the increase in this threshold, measured in PD patients vs. controls, is reversed by PPN DBS, stressing the key role of PPN in the modulation of spinal cord excitability, presumably by controlling the activity of the BG-brainstem descending system. Electrophysiological recordings in PD patients showed that PPN DBS has a dual effect on STN neuron firing: it decreases the discharge activity of bursty neurons while it increases that of non-bursty (irregular or regular) neurons (Galati et al., 2008). This publication argues that the effect on bursty STN neurons might corroborate the therapeutic role of PPN DBS, whereas that on non-bursty neurons might interfere with a favorable outcome on motor signs, justifying the association of PPN and STN DBS rather than PPN alone. Preliminary PET findings from Strafella et al. (2008) show that unilateral PPN DBS (70 Hz) in one PD patient induced significant increase in rCBF in the ipsilateral putamen, cerebellum, insular cortex and bilaterally in the thalamus. However, this study did not allow establishing whether those changes were in relation with the observed slight improvement in motor performance.

3.3.5. Concluding remarks

Tens of thousands of PD patients have now been implanted with stimulation electrodes in different brain structures, including STN, thalamus, GPi and PPN (Temel and Visser-Vandewalle, 2006). It appears that each target has its own specific stimulation-related positive and negative effects, or no effect. Other targets are being investigated in experimental animals, such as the posterior hypothalamic region, whose DBS has been recently reported to reverse haloperidol-induced catalepsy and suggested to be a promising approach to akinesia/bradikinesia (Jackson et al., 2008). The diversity of targets, given the diversity of the disease expression, allows patient-specific selection of the most appropriate one. Such diversity argues for a network rather than a focused effect of DBS. On the other hand, the DBS frequency producing positive effects seems to vary in relationship with the functional state of the target structure and there is a clear need to optimize the stimulation parameters for each new target.

4. Deep brain stimulation and movement disorders

4.1. Dystonia

Dystonia is characterized by involuntary muscle contractions causing twisting and repetitive movements and abnormal postures (Fahn, 1988). It affects few (focal dystonia) to most (generalized dystonia) of the muscle groups of the body with variable severity. Etiological classification includes two wide categories: primary (or idiopathic) and secondary (or symptomatic). Primary dystonias, especially generalized, are often hereditary and respond poorly to medical treatment. Their pathophysiology is still unclear, but an abnormal BG-mediated modulation of cortical motor outflow has been involved. In particular, several lines of evidence suggest a reduced pallidal inhibition of the thalamus and subsequent alteration of cortical motor planning and executive areas, and abnormal regulation of brainstem and spinal cord inhibitory interneuron mechanisms Secondary dystonias usually involve brain damage (due in some cases to diseases of the nervous system), or to less identified causes such as chemical imbalance. In particular, focal dystonia can arise after a trauma, or is induced by certain drugs (Berardelli et al., 1998; Tisch et al., 2007).

4.1.1. Clinical evidences

Surgical management of dystonic patients has been under consideration since the 1950s with several targets being explored, including different thalamic regions, the subthalamic area (namely, the ZI and the field of Forel H1 and H2) and the GPi (Kupsch et al., 2003). Pallidotomy gained renewed interest in the 1990s and several reports confirmed its efficiency on dystonic symptoms, with best results in patients with primary dystonia (Roubertie et al., 2000). Soon after, the successful application of DBS in PD and essential tremor led to the introduction of DBS for the treatment of dystonia. GPi DBS rapidly emerged as a promising approach, while results of DBS of thalamus were less reliable. The

adaptability and reversibility of DBS encouraged the first trials of GPi stimulation in children with severe primary dystonia, which showed a striking and long-lasting efficacy (Coubes et al., 1999; Roubertie et al., 2000). GPi DBS has been reported to also improve generalized or focal severe dystonia in adult patients (Krauss et al., 1999; Krauss, 2002; Kumar et al., 1999a). Recent controlled blinded studies have confirmed the efficacy and safety of GPi DBS for the treatment of patients with primary generalized or segmental dystonia (Vidailhet et al., 2005; Kupsch et al., 2006). GPi DBS is also considered for the management of patients with secondary dystonia, although they may not respond to this treatment as robustly and consistently as patients with primary dystonia (Cif et al., 2003). A recent report, however, indicates that bilateral GPi-DBS is a good therapeutic option for the long-term relief of tardive dystonia due to exposure to neuroleptic drugs (Sako et al., 2008).

Although GPi DBS has become a standard in the management of medically refractive dystonia, its action mechanisms still remain unclear. Contrasting with the rapid benefits provided by DBS on parkinsonian signs such as tremor, clinical improvement of dystonia by GPi DBS is delayed and can progress up to a year after surgery (Krauss, 2002; Roubertie et al., 2000). However, once the response is established, the worsening and return to maximum benefit after turning the stimulus OFF and ON, respectively, is much faster, usually taking only hours. One explanation is that GPi DBS may trigger progressive reorganization of neural circuits and drive the activity within the remodeled network (Tisch et al., 2007). Physiological and imaging studies support the concept of such neural remodeling, by showing short-term and long-term effects of DBS on motor cortex and subcortical circuits, including progressive changes of spinal and brainstem excitability. It has also been noted that the management of dystonia generally requires higher stimulation voltage and pulse width than for PD or tremor patients, resulting in a shorter life of the stimulator's battery. Several reports have explored the use of lower DBS frequency, showing that 60 and 80 Hz are well tolerated and provide satisfactory effects in patients with primary dystonia (Alterman et al., 2007a, 2007b).

Another line of clinical investigation about DBS for dystonia has focused on the exploration of alternative brain targets. STN has been designed following the observation that its DBS in PD patients improves both *on* and *off* state dystonia. The literature available about the outcome of STN DBS supports the validity of this target and encourages further investigations (Kleiner-Fisman et al., 2007; Novak et al., 2008; Tagliati et al., 2004), suggesting that STN would have some advantages over GPi, including a more rapid response and thus a quicker selection of the most suitable parameters (Sun et al., 2007), but these results need to be further confirmed.

4.1.2. Experimental evidences

The effects of HFS of the EP, the rodent homologue of GPi, have been investigated in the dt^{sz} hamster, a model of idiopathic paroxysmal non-kinesiogenic dystonia. Bilateral EP HFS was reported to significantly improve dystonia in a reversible manner, stressing the pathophysiological role of the EP in the dt^{sz} hamster and the suitability of this model to further investigate the mechanisms of HFS in dystonia (Harnack et al., 2004a).

4.2. Essential tremor

Essential tremor is one of the most common movement disorders (Wenning et al., 2005). It is characterized by rhythmic shaking of the arms in 95% of cases, but may also involve tremor of the head, tongue, lower limbs, voice and face. Although generally described as a "benign" disorder, it causes significant functional disability in a majority of patients, and about half of them have medication-resistant symptoms. Essential tremor is usually considered as a monosymptomatic movement disorder of apparent Mendelian autosomal dominant inheritance, though no disease-causing genes are yet certain. The situation seems however more complex, since it seems to occur along with other movement disorders more often than expected, and over 50% of cases reported in the literature have not had an affected family member (Nahab et al., 2007). Neurophysiological studies have suggested the implication of a neuronal network involving the thalamus, the sensorimotor cortex, the inferior olivary nuclei, and cerebellum in the pathophysiology of essential tremor. This view is supported by the clinical observation that ablation or lesions of the VIM, STN or cerebellum can reduce essential tremor. Recent neuropathological studies have reported changes consistent with a degenerative process, and have led to distinguish two types of patients: those with degenerative changes in the cerebellum and those with brainstem Lewy bodies and relatively preserved cerebellum (Louis and Vonsattel, 2008).

DBS has been used to treat various tremor disorders for several decades, notably those medication-resistant (Lyons and Pahwa, 2008). The VIM of the thalamus is the most common DBS target for tremor disorders. This surgical treatment has been consistently reported to result in significant benefit in upper extremities, as well as head and voice tremor, all of which are improved more significantly with bilateral procedures. These benefits have been demonstrated lasting for several years. Surgical complications are relatively uncommon and are generally less frequent than those seen with thalamotomy. Stimulation-related secondary effects are usually mild and are resolved with the adjustment of stimulation parameters. DBS is thus considered as a relatively safe and effective treatment for medication-resistant, disabling essential tremor, but may also have some role in medication-resistant, disabling essential tremor associated with multiple sclerosis and traumatic head injury. More recent studies have demonstrated that DBS of STN and of the subthalamic area, covering the ZI and prelemniscal radiation, also provides benefits in the treatment of essential tremor, with results even more favorable than DBS of the thalamus (Hamel et al., 2007; Herzog et al., 2007a; Lind et al., 2008).

4.3. Huntington's disease

Huntington's disease (HD) is an autosomal dominant, inherited and rare neurodegenerative disease, whose core neuropathology involves the degeneration of the projection neurons of the caudate-putamen. Like other movement disorders involving the BG, HD affects motor, cognitive, and psychiatric functioning. The motor symptoms associate chorea and other hyperkinetic (dystonia, myoclonus) as well as hypokinetic (bradykinesia) disorders that are poorly responsive to pharmacological therapy.

The efficiency of GPi DBS to alleviate dystonia and L-DOPA-induced dyskinesias, designed GPi as a possible anatomical target for the treatment of HD. Moro et al. (2004) reported the first case study showing that bilateral GPi DBS has indeed the potential to improve chorea. There are now other case reports confirming this view and further indicating that chronic GPi DBS can provide long-term and sustained alleviation of HD-associated choreoathetosis and improve daily quality of life in patients with no major cognitive impairment (Biolsi et al., 2008; Hebb et al., 2006). However, precise selection criteria, optimal electrode placement and stimulation parameters remain to be defined, and the therapeutic mechanisms are still unclear. Whereas clinical data point to GPi, the current view of the pathophysiological functioning of BG in HD rather designs GPe as a target for DBS. GPe is thought to be overactive in HD due to the loss the inhibitory input from striatopallidal neurons. Accordingly, experimental evidence has been provided that DBS of GPe improves motor and cognitive

disturbances in a transgenic mice model of HD (Temel et al., 2006a). A computational model in non-human primates, taking into account that a majority of GPe efferents project through GPi to the STN, suggested that GPi DBS has broad network effects, with functional consequences depending on the relative proportion of GPe and/or GPi efferents involved by the stimulation (Johnson and McIntyre, 2008).

4.4. Conclusions

Surgical treatment by DBS is today recognized as an efficient therapeutic option for movement disorders, which can provide substantial benefits sustained in the long-term. Besides PD, it is routinely used for dystonia and essential tremor, the main targets being the GPi and the thalamus, respectively, and it also holds promise for alleviating motor disabilities of HD. For these disorders, other possible targets are emerging, with STN appearing as a network hub, and it is clear that further investigations are needed to define the best ones and the optimal stimulation parameters. Compared to the great strides made in terms of therapeutic applications, progress in our understanding of the action mechanism of DBS remains poor, and more generally this failure points to our still little knowledge of the pathophysiology of these disorders.

5. Deep brain stimulation and psychiatric disorders

Tourette syndrome, OCD, and treatment-resistant depression (TRD) are the three major disorders currently under investigation with DBS in psychosurgery (Larson, 2008). For these psychiatric disorders, as for movement disorders, there was sometimes a background of responsiveness to lesioning procedures that provided the rationale for their treatment by functional surgery and the basis for some target selection. The identification of new candidate targets, although limited by the lack of well-validated experimental models, should benefit from advances in functional neuroimaging in patients and from results of DBS used to treat other diseases. It is however important to note that, for some targets, only a few cases have been reported and negative or side-effects are usually not published. It should therefore be taken into account that there might be a bias in publications related to the effects of DBS for these various pathologies.

5.1. Depression

Depression is a serious mental disorder for which pharmaceutical treatments or electroconvulsive therapy can meet resistance in some patients, as occurs in TRD, and that can lead to suicide in extreme cases. For TRD patients, neurosurgery has been proposed. Procedures such as ablation of the subgenual cingulate or anterior insular cortices have been used. Several other possible targets have been suggested, such as the ventral striatum/NAc, the subgenual cingulate cortex (area 25), the inferior thalamic peduncle, the rostral cingulate cortex (area 24a), and the lateral habenula (Hauptman et al., 2008; Ressler and Mayberg, 2007; Velasco et al., 2005b), and some of them have indeed been tested with the DBS technique. Based on observations that the area Cg25 of the prefrontal cortex was hyperactive in depressed patients (Dougherty et al., 2003), DBS of Cg25 was applied in patients with refractory depression and produced beneficial effects (Mayberg et al., 2005). The area then stimulated corresponds to the white matter tracts adjacent to the subgenual gyrus. Lozano et al. (2008) showed that DBS applied at approximately the same level (that they name the subcallosal cingulated gyrus) had beneficial effects in patients suffering from TRD. One case report highlighted the inferior thalamic peduncle as an efficient target for DBS treatment of depression (Jimenez et al., 2005), and very recently the ventral capsule/ventral striatum (NAc) area has been suggested for TRD (Malone et al., 2009), while other reports show beneficial effects of caudate nucleus DBS (Aouizerate et al., 2004; Schlaepfer et al., 2008).

One classical animal model of depression is the Porsolt test, in which animals are forced to swim until despair since they have no possibility to escape. Using this model, it has been reported that STN DBS worsened the depressive symptoms by reducing the activity of the serotoninergic system (Temel et al., 2007), although the results were not shown for intact animals in this study, but only in a model of PD. This result suggests that STN DBS might be responsible for some depressive signs that are frequently reported in PD patients subjected to STN DBS that can even lead to suicides (Burkhard et al., 2004; Soulas et al., 2008).

5.2. Motivational dysregulation and addiction

When investigating the effects of STN manipulation on cognitive functions in the attentional task or in the delay discounting task, we have mentioned a possible increased motivation for food reward. The anatomical connections of STN in the limbic loop suggest that manipulating the STN should affect motivational processes. We have assessed whether or not STN lesions affect primary processes of motivation by measuring food intake, checking if STN lesions increase hunger. We have shown that whatever the internal state of the animals (deprived or sated) or the reward (standard animal food, palatable food, alcohol or i.v. injection of cocaine), STN lesion does not affect consummatory processes (Baunez et al., 2002, 2005; Lardeux and Baunez, 2008). When assessing incentive motivation by measuring the reactivity to stimuli predicting food, we found that STN lesion increases the responses to these stimuli (Baunez et al., 2002). This result was further confirmed by Uslaner and Robinson (2006). As illustrated in Fig. 19, we also showed that STN lesions increase willingness to work on a lever to obtain food pellets and increase the score of preference for an environment previously associated with food (Baunez et al., 2005). In contrast to these results, we found the opposite effects when the reward was cocaine, highlighting a possible role for STN to modulate the reactivity of the reward system with regard to the nature of the reward involved (Baunez et al., 2005). In a recent study testing the effects of STN lesions on motivation for alcohol, we have further shown that STN lesions could also affect motivation in an opposite manner depending on the initial preference of the animals for the reward (Fig. 19) (Lardeux and Baunez, 2008). It thus appears that STN might be an interesting target where motivation for cocaine and other rewards can be dissociated. Since one of the major challenges to treat cocaine addiction is to reduce the motivation for the drug without decreasing motivation for everything, inactivation of the STN might prove to be an interesting strategy for the treatment of cocaine addiction.

Of course, when referring to motivation, the NAc is classically considered as the critical structure to address. However, although inactivation of the NAc might be an interesting hypothesis in order to reduce motivation for drugs, it might reduce motivation for everything else, reducing the general motivational state of the subject (apathy). DBS of the NAc has been tested in alcoholics with a positive effect on alcohol addiction (Kuhn et al., 2007a). In the rat, it has been shown that NAc DBS could reduce place preference for heroin, but has not been assessed for other types of rewards (Liu et al., 2008). In contrast, DBS of the NAc shell was shown to reduce cocaine-reinstatement seeking behavior, while DBS applied at the level of the dorsal striatum did not show the same effect (Vassoler et al., 2008). Interestingly, without illustrating the result, the authors mention that NAc shell DBS does not affect food-reinstatement seeking behavior. However, in contrast to STN

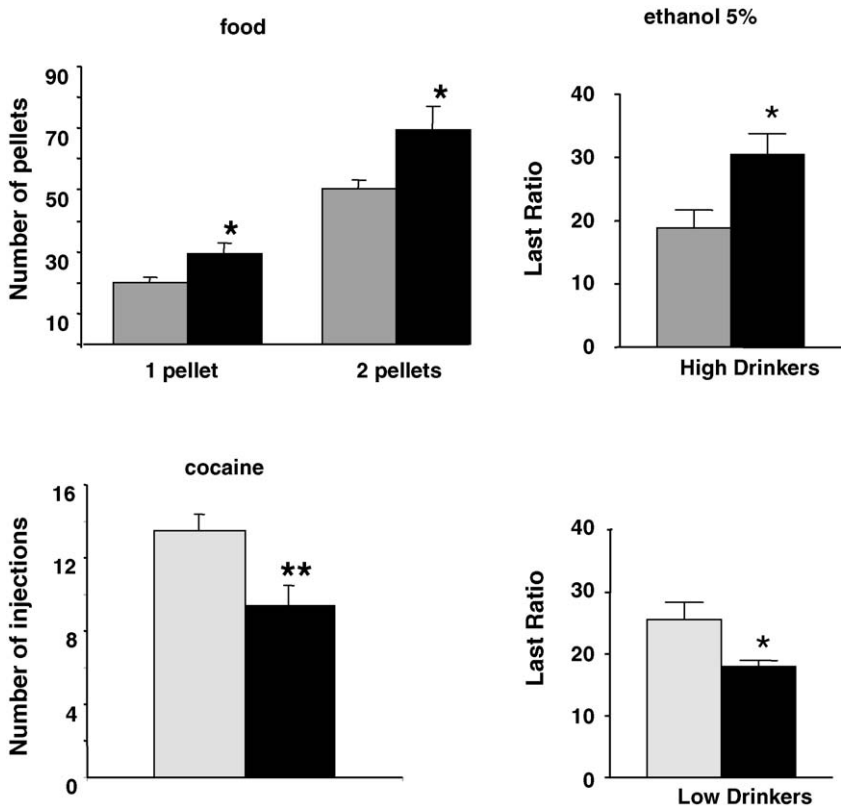

Fig. 19. Effects of STN lesions on motivation for food, cocaine and alcohol. The performance illustrated here relates to the willingness to work for the given reward in a progressive ratio schedule of reinforcement, where the animals have to produce an increasing effort to obtain the reward. When the reward was 1 or 2 food pellets (food), STN lesioned rats (black bars) obtained more rewards than sham-control animals (dark grey bars). In contrast, when working for intra-venous cocaine infusions (250 μg/infusion), STN lesioned rats (black bar) worked less than controls (grey bar) and obtained less infusions. When ethanol 5% was the reward, STN lesioned rats (black bars) belonging to the "high drinker" group worked more (higher ratio completed) than the controls (dark grey bar), while those belonging to the "low drinker" group worked less than their respective control group (grey bar). *, **: significant difference from the sham-control group, $p < 0.05$ and 0.01 respectively (Baunez et al., 2002, 2005; Lardeux and Baunez, 2008).

HFS, DBS in the NAc shell does not allow individual adjustment of the intensity, since there was not any obvious behavior that could allow setting the threshold for each individual. This issue remains to be investigated further.

The cortex has also been the site of stimulation in the context of motivation. It has been shown that self-stimulation into the medial prefrontal cortex, applied before testing motivation for cocaine or food, decreases motivation for cocaine, as assessed by measuring drug seeking in extinction or in progressive ratio whatever the frequency (high or low), with no effect on motivation for food (Levy et al., 2007).

It thus appears that DBS is a promising tool that is only starting to be explored and used in the field of motivation and addiction, and might lead to a new surgical strategy for the treatment of some forms of addiction.

5.3. Obsessive–compulsive disorder

OCD is a psychiatric disorder characterized by obsessional ideas, compulsive behaviors and rituals. The prevalence of this disease is of 1–3%. Currently, the most commonly used treatment combines serotonin-reuptake inhibitors and cognitive therapy, although neuroleptics are also used, as well as clonidine (α_2 receptor agonist) or noradrenergic reuptake inhibitors (Chamberlain et al., 2005). However, there is a proportion of approximately 30% of patients resistant to these treatments (Bjorgvinsson et al., 2007).

In the surgical approach for OCD treatment, the targets for tractotomies or ablative surgery include subcaudate tractotomy, cingulotomy, limbic leucotomy, and anterior capsulotomy (Burdick et al., 2009). However, regarding DBS surgical targets for OCD, two major sites have been studied. The first is the internal capsule extending towards the NAc/ventral striatum. In the first study reporting the effects of DBS applied in OCD patients, the stimulating electrodes were declared to be located in the internal capsule (Nuttin et al., 1999). Further studies specified more precisely the location of the electrodes inducing efficient effect on OCD scores, and they happened to be in an area encompassing the internal capsule and the NAc (Nuttin et al., 2003). Since then, there has been a consensual choice for the anterior limb of the internal capsule as a target for the treatment of OCD with good success (Greenberg et al., 2006). Interestingly, it has been shown that when the shell of the right NAc is targeted, it provides reduction of OCD (Sturm et al., 2003). There are now long-term studies reporting beneficial effects of DBS in the internal capsule/NAc area in OCD patients (Greenberg et al., 2008). In line with these clinical reports, an animal study has shown that DBS of the NAc applied at low frequency in rats decreases spontaneous alternation in a T-maze, this latter behavior being considered as a model of OCD by the authors (van Kuyck et al., 2003). It was also recently shown NAc stimulation could reduce the schedule-induce polydipsia, which is also considered as an animal model of compulsive behavior (van Kuyck et al., 2008). In this study there was, however, no difference in the effects on polydipsia if the stimulation was applied either in the NAc, the medio-dorsal thalamus or the bed nucleus of the stria terminalis.

The second major target for OCD treatment is the STN, based on the observation that STN HFS had beneficial effects on OCD

symptoms in PD patients suffering from OCD as well (Fontaine et al., 2004; Mallet et al., 2002). Recent experimental studies have also focused on STN as a possible DBS target for OCD and used animal models of this pathology. However, it is important to note that there is to date no satisfactory animal model of OCD; therefore one may find reference to OCD in studies measuring stereotyped behavior, for which the obsessive and affective components are not always easy to assess. For example, it has been shown that STN lesions induce perseverative lever presses called "compulsive" lever presses (Winter et al., 2008a). This result is in line with perseverative behavior described previously after STN lesions in an attentional task (Baunez and Robbins, 1997). In contrast, in the monkey, it has been shown that STN HFS of the anterior part of the STN can reduce stereotyped behavior induced by injections of bicuculline into the limbic territory of the GPe (Baup et al., 2008). STN HFS could have a beneficial effect in checking behavior induced by quinpirole, a model that is considered by the authors as a rat model of OCD (Winter et al., 2008c). In line with the former observation in PD patients with OCD, a recent multi-group clinical study confirmed the STN, and particularly its anteromedial part, as a good target for the treatment of OCD. However, beside these positive effects, STN DBS also induced side-effects such as hypomania or anxiety (Mallet et al., 2008). It is however interesting to note that lesion studies have highlighted a role of STN in impulse control and suggested that STN lesion could induce a lack of impulse control in rats, a perseverative behavior (Baunez and Robbins, 1997), by preventing their ability to stop an ongoing action in a stop signal RT task (Eagle et al., 2008). This is in contrast with the beneficial effect of STN DBS to treat OCD. However, in another task appropriate to measure impulsivity, where the animals are given the choice between a small but immediate reward and a large but delayed reward, STN lesioned animals were able to overcome their impulsivity to wait for a bigger reward (Winstanley et al., 2005). These results suggest a specific role of STN in the control of inhibition that can be under the influence of the outcome, as confirmed recently by Uslaner and Robinson (2006).

5.4. Tourette syndrome

Tourette syndrome is a chronic neuropsychiatric disorder of typical childhood onset, characterized by motor and phonic (vocal) tics and coprolalia, commonly associated with behavioral abnormalities, notably symptoms of attention-deficit hyperactivity disorder, obsessive–compulsive behavior, self-injurious behavior, anxiety and mood disorders (Ackermans et al., 2008). Symptoms often improve or completely resolve near adulthood, but persist in a number of patients. The neuronal circuitry underlying this disorder and the pathophysiology are not well understood. Although there is a large body of evidence suggesting abnormal BG function in Tourette syndrome, in particular dysfunction of the limbic BG–thalamocortical system, it remains debated which parts of the BG or their extensive connections with cerebral cortex are responsible for tics. Similarly, there is little specific information on the neuronal circuitry responsible for comorbid symptoms commonly associated with Tourette syndrome. Several attempts using ablative surgical procedure have been made to treat patients debilitated by Tourette syndrome despite medical therapy, with targets including the frontal lobe, the cingulate cortex, the thalamus, the pallidum, the ZI and the cerebellum (Temel and Visser-Vandewalle, 2004). However, the target localization in many cases was questionable and the results were often unsatisfactory, or showed major side-effects, such as hemiplegia or dystonia. The thalamus has been the first and remains the structure the most frequently targeted for the treatment of intractable Tourette syndrome by DBS. Vandewalle et al. (1999) reported successful thalamic HFS in a patient with severe Tourette syndrome using target selection based on thalamotomy described by Hassler and Dieckmann (1970). The trajectory used allowed stimulation through one electrode of three thalamic components: the centromedian nucleus as part of the intralaminar group, the substantia periventricularis as part of the midline nuclei, and the nucleus ventrooralis internus. The same group then described the long-term benefits of bilateral thalamic HFS on the tics in three patients (Visser-Vandewalle et al., 2003), and noted the occurrence of some side-effects. Recent trials confirmed the validity of the thalamic target (Bajwa et al., 2007; Maciunas et al., 2007; Servello et al., 2008). Notably, DBS targeting the CM/Pf and ventralis oralis complex of the thalamus showed good (but also variable) responses of patients, decrease of comorbid symptoms and no permanent side-effects (Servello et al., 2008).

Case reports have also pointed to encouraging results of DBS of the GPi, with a substantial reduction of tics and associated behavioral symptoms (compulsions), confirming the role of the dysfunction of limbic BG–thalamocortical systems in this disorder (Ackermans et al., 2006; Diederich et al., 2005; Houeto et al., 2005). The combination of thalamic CM/Pf and GPi stimulation does not seem to provide additional benefits (Houeto et al., 2005; Welter et al., 2008). Other targets include the anterior internal capsule and the NAc (Flaherty et al., 2005; Kuhn et al., 2007b), which has reported providing major alleviation of tics involving self-injury, and suppression of coprolalia (Kuhn et al., 2007b). A review on the clinical trials of DBS for Tourette syndrome (Mink et al., 2006) estimated that data were insufficient to recommend one site over the others and pointed to the importance of postoperative imaging to accurately identify the final electrode location, since the regions targeted comprise small nuclei (thalamus) or multiple functionally distinct subcircuits (GPi, NAc).

5.5. Conclusions

In this section we have reviewed some of the major psychiatric disorders for which DBS has already been attempted with relative success depending on the disease. The general idea is that DBS interferes with the circuitry in which the targeted structure is involved, leading to the various sites studied for the given disorders. For instance, the NAc area has been chosen for the treatment of a disease such as OCD, which is also related to dysfunction of the prefrontal cortex and, interestingly, a recent study (McCracken and Grace, 2007) has shown that NAc DBS modulates the activity of the orbitofrontal cortex.

6. Deep brain stimulation and epilepsy

Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures, affecting 0.5–1% of mankind. An epileptic seizure is caused by an excessive and/or hypersynchronous electrical neuronal activity, which can affect a specific brain area or structure (focal seizure), or can be largely distributed (generalized seizures). Usually seizures are self-limiting and can manifest as an alteration in mental state, tonic or clonic movements, convulsions, and various other psychic symptoms (such as *déjà vu* and *jamais vu*, or absence seizures). Most forms of epilepsy are lifelong, but some of them are confined to childhood. Epilepsy is difficult to classify, since each syndrome has its own unique combination of seizure type, age of onset, treatment, EEG features and prognosis. The most used classification criterion relies upon the localization of the seizures in the brain (such as temporal lobe epilepsy, generalized epilepsy, etc.), but epilepsy syndromes can also be classified by their presumptive cause (idiopathic, symptomatic and cryptogenic), and those characterized by generalized seizures are divided according to the effect on the

body (absence, myoclonic, clonic, tonic, tonic–clonic and atonic). Experimental models of epilepsy used for DBS studies include spontaneous generalized non-convulsive absence seizures and kindling, which is a technique for inducing seizures by stimulating specific brain structures.

6.1. Clinical data

The clinical use of DBS is justified for medically refractory epilepsy when patients do not meet the criteria for resective brain surgery. In general, these patients have long history of frequent motor seizures that resist pharmacological treatments, leading to an impaired quality of life due in particular to seizure-induced injuries. DBS appears to be safe and well tolerated, while its effectiveness is variable. It should be noted, however, that DBS is still considered an experimental therapy for epilepsy (Halpern et al., 2008), since the clinical outcome is still based on small samples of a few pilot studies on little cohorts of patients. Clinical electrical stimulation for epilepsy has the peculiarity that can be delivered according to either a predefined schedule independent of physiological activity (open-loop manner), similarly the "classical" DBS, or in response to EEG activity (closed-loop or responsive stimulation). Osorio et al. (2005) have demonstrated in four patients the therapeutic efficacy of closed-loop stimulation, which was delivered both directly to the epileptogenic zone (local closed-loop) and indirectly through the anterior thalami (remote closed-loop).

The earliest report of applying electrical stimulation to the brain to treat seizures in humans was provided in the 1950s by Penfield and Jasper (1954). They observed that acute focal electrical stimulation of the exposed cortex resulted in flattening of the local EEG (both normal rhythms and spontaneous epileptiform discharges). This gave rise to the idea that focal stimulation of a cortical epileptic focus might disrupt seizures. Accordingly, a recent case report (Elisevich et al., 2006) showed 90% reduction of seizure frequency in a patient by focal open-loop stimulation of the cortex originating seizures (dorsolateral convexity). However, stimulation of the superficial cortex can hardly be referred to as DBS, thus our review on stimulation of cortical structures for epilepsy will focus only on hippocampus (for a recent review on cortical stimulation for the treatment of epilepsy see Sun et al., 2008).

The hippocampal formation belongs to the Papez circuit, a group of limbic structures with demonstrated role in epilepsy, and has been historically implicated in the initiation and propagation of temporal lobe epilepsy (Swanson, 1995). Abolition of generalized tonic–clonic seizures and decrease of interictal EEG spikes at the epileptic focus has been shown in 7 out of 10 patients with intractable temporal lobe seizures by subacute open-loop hippocampal stimulation (Velasco et al., 2000a). Three of these patients were then tested for short-term memory, which was not affected by DBS (Velasco et al., 2001b). Another study on seven patients reported >50% reduction in interictal spikes in six patients, with a ≥50% reduction in three of them, by amygdalo-hippocampal DBS (Vonck et al., 2005).

Another brain target for DBS in the context of epilepsy is the cerebellum. In the early 1970s, Cooper and colleagues provided the first reports of cerebellar DBS for the treatment of epilepsy (Cooper, 1973; Cooper et al., 1973). The rationale for targeting this structure arose from previous experimental data showing an effect of cerebellar stimulation on seizures (Cooke and Snider, 1953; Moruzzi, 1941, 1946). Cerebellar stimulation likely activates inhibitory Purkinje neurons, which results in the reduction of cerebellar excitatory output to the thalamus, and from the thalamus to the cortex. Davis and colleagues have reported benefits of using cerebellar DBS since the 1970s, showing seizure improvements on average in more than 50% of the treated patients (Davis et al., 1983; Davis and Emmonds, 1992). More recent papers have reevaluated this technique. For example, Velasco et al. (2005a) reported ~60% reduction of recurrent generalized tonic–clonic seizures in five patients treated by DBS of the superomedial cerebellar cortex.

Several other brain targets for DBS showed some degree of success in epileptic patients: the thalamus (centromedian nucleus and anterior thalamus), the STN and the caudate nucleus (Halpern et al., 2008; Pollo and Villemure, 2007; Salanova and Worth, 2007). The centromedian nucleus of the thalamus belongs to a subcortical reticular system arising from the brainstem and projecting to the cortex, thus it is likely to be involved in the pathophysiology of generalized seizures. Accordingly, DBS of this structure has been shown to improve seizure control, presumably by desynchronizing and hyperpolarizing neurons of this ascending pathway and of the target cortex (Velasco et al., 2000b, 2007). The anterior thalamic nucleus is part of the above-mentioned Papez circuit, and its stimulation can affect wide regions of the cortex and has been reported to improve seizure control (Franzini et al., 2008; Kerrigan et al., 2004; Lim et al., 2007). The rationale for targeting STN is to reduce its excitatory output to the SNr, which plays a role in generalized seizure propagation through its projections to the superior colliculus, as suggested by several experimental works (Dybdal and Gale, 2000; Gale, 1986; Gale et al., 1993). Some open-label studies on single or few patients have shown significant improvement of seizure by STN HFS. For example, Chabardes et al. (2002) obtained ~64% improvement of seizures in four out of five patients, while less encouraging results were obtained in two patients (≤50%, without improvement of seizure-related injuries in one case) by Handforth et al. (2006).

On a clinical point of view, the mechanisms by which DBS improves epilepsy remain to be elucidated and are presumably variable depending on the stimulated brain structure. Thus, it is difficult as yet to make definitive judgments about the efficacy of DBS for seizure control, as well as on the target to be stimulated, since it also depends on the anatomical and functional nature of the epilepsy that needs to be treated by DBS. Further studies are necessary to identify patient populations for whom this technique would be indicated, to define the most efficacious target in relationship with the specific kind of epilepsy, to set the optimal stimulation parameters, and finally to identify the action mechanisms.

6.2. Evidences from experimental models

Among the first experimental reports on DBS applied for epilepsy, STN HFS was studied in rats exhibiting spontaneous generalized non-convulsive absence seizures, characterized by bilateral and synchronous rhythmic spike-and-wave discharges on cortical EEG recordings and concomitant behavioral arrest (Vercueil et al., 1998). In this model, STN HFS was able to suppress such absence seizures, suggesting the involvement of BG in the control of generalized seizures. Using the same rat model of absence epilepsy, Feddersen et al. (2007) showed that a single 5 s HFS of the SNr interrupted ongoing epileptic discharges. However, SNr HFS applied with different time protocols (continuously ON; 5 s ON, 5 s OFF; 5 s ON, 15 s OFF) was not antiepileptic because of a refractory period of about 60 s after the stimulation. SNr HFS has also been tested against amygdala-kindled seizures, and it could block them in half of the treated rats (Shi et al., 2006a).

Encouraging results by stimulating the anterior thalamic nuclei were obtained by Hamani et al. (2004): this treatment significantly prolonged the latency for developing pilocarpine-induced seizures and status epilepticus. More recently, it has also been shown that the anticonvulsant effects of anterior thalamic nuclei DBS in this model were mainly determined by the current and not the frequency of stimulation (Hamani et al., 2008). In another rat

model of epilepsy (pentylenetetrazol-induced seizures), anterior thalamic nuclei DBS could delay the onset of EEG seizures, probably via an enhanced release of norepinephrine in the anterior and posterior thalamus (Ziai et al., 2005), and by a mechanism possibly involving an increase of serotoninergic activity in the anterior thalamic nucleus itself (Mirski et al., 2009).

Concerning the cortex, a recent experimental study reported some effects on piriform cortex kindled seizures depending on the pattern of LFS delivered in the central piriform cortex (Ghorbani et al., 2007): application of different patterns of LFS before kindling stimulation had no anticonvulsant effect, but it could exert an inhibitory effect when applied during an inter-seizure interval of 7 days. In addition, LFS had an antiepileptogenic effect during kindling acquisition. Moreover, Zhu-Ge et al. (2007) reported that LFS of the ipsilateral and contralateral central piriform cortex decreased the incidence of generalized amygdaloid-kindled seizures (ipsilateral LFS also shortened cumulative generalized seizure duration). The mechanism proposed for such inhibition of seizures implies a reduction of after-discharge duration, generation and propagation.

Stimulation of the ventral hippocampus in the rat during the hippocampal kindling process also gave positive results: reduced expression of seizures in some animals, and increased refractoriness for subsequent seizures in all of them (Cuellar-Herrera et al., 2006). Using a similar model, Wyckhuys et al. (2007) showed that hippocampal HFS can reduce the excitability of the kindling target zone, thus providing a possible mechanism for such DBS. Another possible mechanism underlying the positive effects of hippocampal LFS (1 Hz) in the amygdala-kindling process could involve an increased binding of benzodiazepine receptors and decreased binding of μ opioid receptor (Lopez-Meraz et al., 2004).

In the pentylenetetrazol-induced seizures model, Nishida et al. (2007) showed that intermittent stimulation of the histaminergic tuberomammillary nucleus was effective in desynchronizing EEG. On the other hand, DBS of this structure in the rat had negative effects against amygdaloid kindling: both HFS and LFS led to the exacerbation of the features of kindling-generated seizures (Wu et al., 2008). Finally, a recent report showed reduction of seizures triggered by amygdaloid kindling by LFS of the cerebellar fastigial nucleus (Wang et al., 2008).

In conclusion, while several papers, especially in these last 2 years, have addressed the issue of DBS for antiepileptic therapy, further work is needed to identify the best targets to be stimulated in relation with the different types (or models) of epilepsy, and the mechanisms also remain to be elucidated.

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