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CHAPTER 12

Effects of GPi and STN inactivation on physiological, motor, cognitive and motivational processes in animal models of Parkinson's disease

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Abstract: Loss of the dopaminergic input to the striatum, characterizing Parkinson's disease, leads to the hyper-activity of two key nuclei of the basal ganglia (BG): the subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi). The anatomo-physiological organization of the BG and their output suggested that interfering with such hyper-activity could restore motor function and improve parkinsonism. Several animal models in rodents and primates, as well as clinical studies and neurosurgical treatments, have confirmed such hypothesis. This chapter will review the physiological and behavioural data obtained by inactivating the GPi or the STN by means of lesions, pharmacological approaches and deep brain stimulation. The consequences of these treatments will be examined at levels ranging from cellular to complex behavioural changes. Some of this experimental evidence suggested new and effective clinical treatments for PD, which are now routinely used worldwide. However, further studies are necessary to better understand the consequences of GPi and STN manipulation especially at the cognitive level in order to improve functional neurosurgical treatments for Parkinson's disease by minimizing risks of side-effects.

Keywords: Basal ganglia; deep brain stimulation; dopamine; globus pallidus; lesion; substantia nigra; electrophysiology; behaviour

Introduction

The basal ganglia (BG) are a group of interconnected deep brain structures receiving massive glutamatergic inputs from the cortex and the thalamus, mainly via the striatum (caudate/putamen nuclei) and in a lesser extent via the subthalamic nucleus (STN). BG are mainly implicated in motor behaviour and learning, as well as in cognitive and motivational processes. In 1989, Albin et al. synthesized the data available regarding the anatomo-physiological organization of the BG

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and proposed a model functioning via two segregated pathways going from the striatum to the output BG nuclei, that is, the direct and indirect pathways. The output BG nuclei include the internal segment of the globus pallidus (GPi), or entopeduncular nucleus (EP) in rodents, and the substantia nigra pars reticulata (SNr). GPi/EP and SNr are GABAergic structures innervating mainly the motor thalamic nuclei and receiving inputs from the striatum via two major pathways, one directly from the striatum (the direct pathway) and the other (the indirect pathway) via the external globus pallidus (GPe, or GP in rodents) and the STN. This organization has been described for five parallel loops originating from various cortical areas and innervating different sectors of each structure, defining functional segregated loops: the motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal and limbic loops (Alexander et al., 1986). DeLong (1990) further improved this model of the motor loop by introducing the dysfunctions associated with the loss of substantia nigra pars compacta (SNc) neurons producing dopamine (DA), and the ensuing striatal DA depletion characterizing Parkinson's disease (PD). This model, illustrated in Fig. 1 suggested that both the STN and the GPi are hyper-active in PD, leading to akinetic-like symptoms (DeLong, 1990). It became then obvious that an interesting alternative strategy to DArgic treatments for PD could be to reduce this hyper-activity at the level of either the STN or the GPi. This chapter will thus review the physiological and behavioural data obtained using this strategy, using various means of inactivation, that is lesions, pharmacological inactivation or deep brain stimulation (DBS) at high-frequency stimulation (HFS). This latter technique, first applied in the STN of PD patients by the group of Benabid in Grenoble, France (Limousin et al., 1995), is currently used worldwide with great success. However, there are still remaining questions regarding its mechanism of action (Gubellini et al., 2009).

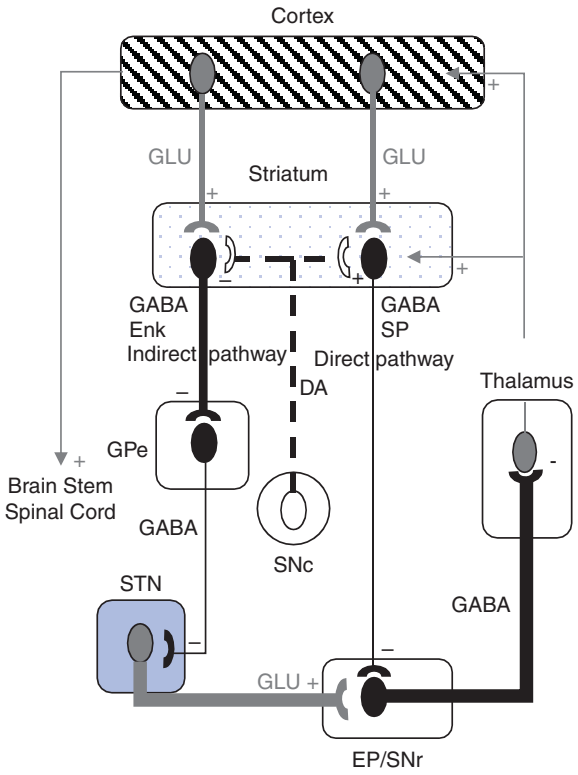

Fig. 1. Schematic diagram of the basal ganglia organization after a DA depletion as proposed by DeLong (1990). This diagram was clearly indicating a hyper-activity of the STN and the GPi, suggesting therefore that normalization of STN or GPi activity could be a beneficial treatment for parkinsonism. STR, striatum; STN, subthalamic nucleus; GPe, external segment of the globus pallidus; EP, entopeduncular nucleus (=GPi: internal segment of the globus pallidus); Pf, parafascicular nucleus of the thalamus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; GLU, glutamate; Enk, enkephalin; SP, substance P.

During the last 50 years, several different animal models of PD have been developed to better understand the pathophysiological mechanisms of this neurodegenerative disorder. Acute models were the first to be introduced by using monoamine depleting agents, such as reserpine (that blocks the vesicular monoamine transporter), and later by using DA receptor antagonists, such as haloperidol. Nowadays, the two most common

and relevant PD models are based on toxins that impair oxidative phosphorylation by inhibiting the complex I of the mitochondria, leading to DAergic neuron loss: 6-hydroxydopamine (6-OHDA), which is injected into the SNc or the striatum of rodents and selectively kills DAergic neurons (after blocking the noradrenaline transporter), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is injected systemically in non-human primates and certain mice strains and is transformed into the toxic product 1-methyl-4-phenylpyridinium that is introduced into DAergic neurons by the DA transporter (Gubellini et al., 2010).

GPi manipulation in PD

Neurons of the EP recorded *in vitro* show a spontaneous action potential discharge activity at frequencies of 4–10 Hz at membrane potentials around –50 mV (Nakanishi et al., 1990; Shin et al., 2007). In primate PD models (MPTP lesion), the discharge activity of GPi neurons changes towards a more irregular pattern characterized by bursts of action potentials, which is consistent with findings in PD patients (Hutchison et al., 1994). There is no consensus about the change in their mean firing rate, which is described as increased (Boraud et al., 1996; Filion and Tremblay, 1991; Wichmann and DeLong, 2003), as well as decreased (Raz et al., 2000), while there is agreement on the apparition of a synchronized low-frequency oscillatory activity (Bergman et al., 1994; Eusebio and Brown, 2007; Filion and Tremblay, 1991; Leblois et al., 2006; McCairn and Turner, 2009; Raz et al., 2000).

Neurophysiological effects

The first experimental report regarding the neurophysiological effects of GPi inactivation was obtained in MPTP-treated macaques, in which GPi neurons became hyper-active. GPi HFS could significantly reduce such hyper-activity, restoring a frequency of action potential discharge similar to that observed in normal animals, and this change was correlated with an improvement of motor symptoms (Boraud et al., 1996). More precisely, the firing of the majority of GPi neurons become time-locked with GPi HFS, showing a first excitatory phase with ~3 ms latency, followed by inhibition (~4.5 ms) and a second excitation (~6.5 ms) (Bar-Gad et al., 2004). Such temporal locking has been also found during GPi recordings in PD patients (Dostrovsky et al., 2000) and supported by computational models (Johnson and McIntyre, 2008). On the other hand, no clear time-lock has been observed in another study on MPTP-treated monkeys (McCairn and Turner, 2009), where the majority of GPi and GPe neurons responded to repeated periods of 30 s GPi HFS with a phasic peristimulus modulation in firing, towards both increases and decreases. A minority of pallidal neurons responded with sustained responses (more common in the GPi) that could last up to the next stimulation period, and nearly all these sustained responses were significant decreases in firing rate. Such differences between findings on the effects of GPi HFS on spike frequency rate could be attributed to the experimental set-up, especially the duration of HFS application. However, the interesting contribution of McCairn and Turner paper is about the role of GPi HFS in suppressing the oscillatory low-frequency activity of pallidal neurons due to DA depletion that characterizes parkinsonian state (Utter and Basso, 2008).

Regarding the effects of GPi HFS in other BG structures, Anderson and colleagues (2003) showed a reduction of discharge frequency in thalamic neurons responding to stimulation applied in intact monkeys. These findings seem in contrast to the schematic functioning of BG, since this treatment should inactivate the GPi and thus disinhibit thalamic activity, but they are supported by evidences from patients receiving GPi HFS for dystonia (Montgomery, 2006). A recent study has also shown that GPi HFS applied in MPTP monkeys time-locks the firing rate of neurons in

the primary motor cortex to the stimulus, increasing the response specificity to passive limb movement (Johnson et al., 2009). This latter observation is in line with the findings in PD patients showing that GPi HFS increased regional cerebral blood flow in the premotor cortex detected by positron emission tomography (PET) (Davis et al., 1997).

There is little data on the neurophysiological effects of EP inactivation in rodents. A recent electrophysiological slice study investigated the effects of EP HFS on EP neurons in the rat, showing that HFS induces an elevation of extracellular K^+, which decreases EP neuron activity by activating a depolarizing ion conductance with no synaptic involvement (Shin et al., 2007). Earlier studies focused on the effects of EP inactivation in the striatum of 6-OHDA-lesioned rats, showing that EP lesion could counteract the increase of preproenkephalin mRNA levels induced by L-3,4-dihydroxyphenylalanine (L-DOPA) treatment (Perier et al., 2003) and that EP HFS had no significant effect on striatal DA transmission (Meissner et al., 2004).

Effects of manipulation of the GPi on motor behaviour

Lesion and pharmacological GPi inactivation in the monkey

One of the first evidences showing that the GPi could represent an interesting target for the treatment of PD was provided by pharmacological experiments showing that blocking glutamatergic transmission within this structure could alleviate motor deficits in monkeys rendered parkinsonian with MPTP (Brotchie et al., 1991; Graham et al., 1990). A similar effect was observed in the unilateral MPTP model of parkinsonian monkey, in which a unilateral GPi injection of MK801, an NMDA receptor antagonist, induced a contralateral circling behaviour similar to that induced by DA agonists (Levy et al., 1997).

Pharmacological inactivation is most often performed by means of infusions of the $GABA_A$ receptor agonist muscimol into the given cerebral structure. It was shown that a focal inactivation of the GPi with muscimol infusions impaired grasping and reaching, affecting velocity (Wenger et al., 1999). These results supported the hypothesis that GPi inhibition disrupts its ability to inhibit competing motor mechanisms and to prevent them from interfering with desired voluntary movement. In a later study where they tested the effects of muscimol infused into various selective areas of the GPi, Baron and colleagues showed that akinesia and bradykinesia induced by MPTP could be alleviated when muscimol was infused into the centromedial part of the sensorimotor GPi (Baron et al., 2002). The same study showed that inactivation of GPi areas outside of the motor territories did not improve parkinsonism but induced circling and behavioural abnormalities.

Only a few studies reported effects of a GPi lesion on behaviour in intact monkeys. One of these studies using kainic acid lesion revealed motor deficits in arm movement performance (Horak and Anderson, 1984), while a study using kynurenic acid (a broad spectrum excitatory amino acid antagonist) showed dyskinesia (Robertson et al., 1989). In the parkinsonian monkey, recent studies using a chemical lesion of GPi confirmed the beneficial effects of GPi inactivation on motor activity and parkinsonian scores (Lieberman et al., 1999; Lonser et al., 1999).

Since, according to the model of the BG (DeLong, 1990), dyskinesias were considered as the result of a decreased inhibitory influence from the GPi to the motor thalamus, it was surprising to find that GPi inactivation could have beneficial effects by reducing L-DOPA-induced dyskinesia. In the marmoset rendered parkinsonian with MPTP, it was indeed shown that a unilateral electrolytic lesion of the GPi could reduce the L-DOPA-induced dyskinesias (Iravani et al., 2005). There are numerous clinical studies dedicated to the beneficial effect of pallidotomy on L-DOPA-induced dyskinesia in parkinsonian patients (Alkhani and Lozano,

2001; Dogali et al., 1994; Laitinen et al., 1992; Vitek et al., 2003).

It is interesting to note that, as suggested by the pathophysiological model of the BG proposed by DeLong (DeLong, 1990), both STN and GPi were possible interesting targets for the treatment of PD. In contrast, GPe inactivation was not predicted to have any beneficial effect. Indeed, according to this model of the BG (Fig. 1), inactivating the GPe would result in an enhancement of the STN hyper-activity and should thus worsen a parkinsonian state. This was indeed confirmed by a study showing that a lesion of the GPe in MPTP-lesioned monkeys worsened their motor symptoms (Zhang et al., 2006).

GPi HFS in the monkey

HFS has been widely applied into the GPi of PD patients but, surprisingly, there are not many animal studies supporting this therapeutical approach. One pioneering work has shown that unilateral HFS of the GPi could improve parkinsonian symptoms such as muscular rigidity and akinesia in unilateral MPTP-lesioned monkeys (Boraud et al., 1996). Although it has been shown that GPi DBS applied in PD patients was efficient for the treatment of L-DOPA-induced dyskinesia (Benabid, 2003; Wichmann and DeLong, 2006), there is no published study to date showing this effect in monkeys.

Lesion and pharmacological EP manipulation in the rat

In the reserpinized model, injection of glutamatergic antagonists into the EP restores locomotor activity (Brotchie et al., 1991). In the same model, or in alpha-MPT model, NMDA antagonists injected into the EP also alleviate muscular rigidity (Klockgether and Turski, 1990). In unilateral DA-depleted rats, lesioning the EP decreased the rotations induced by amphetamine (Olds et al., 2001, 2003) or L-DOPA (Honey and Shen, 1998). This latter result is in contradiction with another study that has shown that EP lesion was unable to correct the circling behaviour induced by L-DOPA in unilateral DA-depleted rats (Perier et al., 2003). On the cataleptic state induced by haloperidol, it was shown that a bilateral excitotoxic lesion of the EP had a beneficial effect (Zadow and Schmidt, 1994).

In the intact rat first, we have shown that bilateral infusions of the NMDA antagonist DL-2-amino-5-phosphonopentanoic acid (AP-5) into the EP could induce an akinetic-like deficit associated with a premature-responding deficit in a simple reaction-time (SRT) task (Baunez and Amalric, 1996). In order to measure the effects of intra-EP bilateral infusions of AP-5 in a rat model of early parkinsonism, we have used the same SRT task allowing a subtle measure of reaction time (RT) (see Fig. 2). In this task, the rats are trained to press a lever down and sustain their paw on the lever until the occurrence of a light, at which they have to release the lever quickly to obtain a food pellet. The RT is the time taken to withdraw the paw from the lever after the onset of the light. Parkinsonian patients suffering from akinesia are known to exhibit increased RT in these tasks. After a bilateral infusion of 6-OHDA into the dorsal striatum, the rats' performance is impaired in terms of correct responses, mainly because of increased RT, resulting in an increased number of delayed responses (non-rewarded responses for which the RT exceeded 600 ms) (Baunez et al., 1995). In this model of rat parkinsonism, we have shown that the same bilateral infusion of AP-5 into the EP alleviates akinetic-like behaviour in the SRT task in the rat, by reducing the number of delayed responses (Baunez and Amalric, unpublished).

EP HFS data in rodents

Probably because of its small size in the rat, the EP has been rarely specifically targeted for

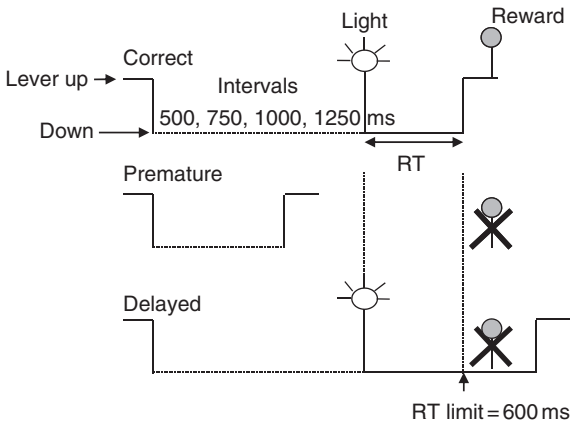

Fig. 2. The simple reaction-time task used in the rat. The rats are trained to press a lever down and sustain their paw on it until the occurrence of a visual stimulus (a light) that may happen at either 500, 750, 1000 or 1250 ms. At the presentation of the light, the rat have to withdraw their paw from the lever as quickly as possible (i.e. reaction time, which has to be below 600 ms) to get a food pellet as a reward. Three types of responses are possible: (1) correct, (2) premature responses when the rat withdraws its paw from the lever before the presentation of the light and (3) delayed responses when the rat withdraw its paw from the lever after the presentation of the light, but with a reaction time exceeding 600 ms.

behavioural studies on EP HFS effects. Only one micro-dialysis study has reported that EP HFS increases DA levels in the striatum concomitantly with DAergic drugs administration (Meissner et al., 2004). It was also shown that EP HFS reduces the number of dystonic attacks in the dystonic dtsz hamster (Harnack et al., 2004).

Effects of manipulation of the GPi on cognition

Unfortunately, no study testing the effects of GPi/EP manipulation on cognitive functions has been published to date, either in monkeys or in rats. Given the clinical reports after pallidotomy or GPi DBS, it would be very interesting to investigate further attentional and executive functions as well as motivation.

This first part dedicated to the GPi revealed that a large body of evidence supported the beneficial effect of pallidotomy or GPi HFS for the treatment of motor deficits in parkinsonism. However, our review of the literature revealed as well a serious lack in investigations of the non-motor functions. Although clinical application of pallidotomy or GPi DBS in the treatment of PD seems to induce modest cognitive side-effects (Rettig et al., 2000; Scott et al., 2002; Trepanier et al., 1998), there are reports of mood changes and weight gain that might be related to the direct consequence of GPi manipulation (Dalvi et al., 1999; Fukuda et al., 2000; Okun et al., 2003, 2009; Ondo et al., 2000). It would therefore be useful to investigate further these observations in animal models.

STN manipulation in PD

The STN belongs to the indirect pathway of the BG, as well as to the so-called hyper-direct pathway from the cortex to the BG output structure through the STN itself. STN is a glutamatergic structure innervating mainly the GPi/EP and the SNr, but also the GPe, the ventral pallidum, the pedunculopontine nucleus, and to a lesser extent the striatum and nucleus accumbens, and also the DAergic nuclei (ventral tegmental area and SNc). The major inputs to the STN arise from various cortical areas (i.e. the hyper-direct pathway), the ventral pallidum and the GPe (the indirect pathway), the parafascicular nucleus of the thalamus, the pedunculopontine nucleus, the dorsal raphe, the ventral tegmental area and the SNc (Parent and Hazrati, 1995a, 1995b). Recent evidence for a direct STN-cortex loop circuit has also been provided (Degos et al., 2009). STN neurons are spontaneously active both *in vitro* and *in vivo*, and fire action potentials at a frequency ranging from <10 Hz up to 20–25 Hz at membrane potentials around –50 to –60 mV, reaching 300–500 Hz at more depolarized potentials. Approximately half of STN neurons have a tonic firing activity, also

called single-spike mode. The other half switch from tonic to burst-like firing pattern, or 'burst' mode, when hyper-polarized. To note that at hyper-polarized membrane potentials (–60 to –70 mV) most STN neurons become silent (Beurrier et al., 1999, 2000; Bevan and Wilson, 1999; Nakanishi et al., 1987; Overton and Greenfield, 1995). These spontaneous firing activities result from phases of cyclic and alternate activation/inactivation of depolarizing and hyper-polarizing currents, with a contribution of pallidal GABAergic inputs (Beurrier et al., 1999; Bevan et al., 2002).

In animal models of PD, a general increase in spike frequency and a shift to a more bursting pattern have been observed *in vivo* in STN neurons, both in 6-OHDA-lesioned rats (Hassani et al., 1996; Hollerman and Grace, 1992; Kreiss et al., 1997; Ni et al., 2001; Tai et al., 2003; Vila et al., 2000) and in MPTP-treated monkeys; in the latter, a low-frequency oscillatory activity in the β band – that in humans is highly correlated with tremor – has also been detected (Bergman et al., 1994, 1998; Bezard et al., 1999; Meissner et al., 2005). Interestingly, the suppression of such oscillatory β activity by STN HFS in parkinsonian patients correlates with the improvement of motor performance (Kuhn et al., 2008).

Neurophysiological effects

Electrophysiology

Electrophysiological studies performed *in vitro* in brain slices of naïve rats have shown that STN HFS decreases and even blocks firing activity of STN neurons (Beurrier et al., 2001) or induces an initial increase in action potential discharge followed by a longer-lasting inhibition (Lee et al., 2003; Magarinos-Ascone et al., 2002). Successive work in slices from reserpine-treated mice showed that spontaneous STN neuron discharge was completely replaced by a stimulation-driven one (mediated by Na^+ and L-type Ca^{2+} channels) at the same frequency of stimulation up to 130 Hz (Garcia et al., 2003). However, it should be considered that the stimulation parameters (pulse duration and intensity) used in these slice studies were adjusted to obtain an electrophysiological response, rather than to be relevant to those used in clinical treatment. Overall, these works support the concept that STN HFS can disrupt the abnormal low-frequency oscillations of STN neurons triggered by DA depletion by imposing a stimulation-driven pattern of spike activity.

We have shown that, in brain slices of 6-OHDA-treated rats, spontaneous glutamate activity recorded from striatal medium spiny neurons was significantly increased (Gubellini et al., 2002), and that 5 days of STN HFS (applied using clinically relevant parameters) could completely reverse these changes and even reduce such activity below control levels (Gubellini et al., 2006). Interestingly, striatal glutamatergic hyper-activity induced by 6-OHDA lesion is also reversed by STN lesions (Centonze et al., 2005), suggesting that similar mechanisms might underlie the synaptic effects of STN lesion and STN HFS.

In MPTP-treated monkeys, STN HFS has been shown to inhibit the mean firing rate of STN neurons and, in parallel, to reduce their low-frequency oscillatory activity (Meissner et al., 2005). STN HFS also evoked spikes in these cells, which were not time-locked to the electrical stimulus, as observed *in vitro*. Concerning the pallidal complex, STN HFS in MPTP-treated monkeys changed the spontaneous irregular firing pattern of both GPe and GPi into a high-frequency and regular pattern (Hahn et al., 2008; Hashimoto et al., 2003). In opposition to these findings, it has been shown that STN HFS regularized and reduced neuronal firing activity in the motor thalamus (Dorval et al., 2008; Xu et al., 2008), suggesting that STN HFS could increase STN output and thus produce inhibitory changes in the thalamus.

Electrophysiological studies performed *in vivo* in 6-OHDA-treated rats have shown that STN DBS, in general, dramatically reduced the firing activity of the majority of neurons of the STN (Shi et al., 2006; Tai et al., 2003), the SNr (Benazzouz

et al., 2000; Tai et al., 2003) and the pedunculopontine nucleus (Florio et al., 2007) and had little effect in the GP (Shi et al., 2006). Concerning the SNr, another study in rats treated with antagonists of DA receptors showed that STN HFS regularized the firing pattern of SNr neurons and normalized their response to cortical stimulation, suggesting that the stimulation restored the balance between inhibitory and excitatory influences on this structure (Degos et al., 2005). Another brain target examined for STN HFS effects in 6-OHDA-treated rats is the dorsal raphe nucleus (DRN), a midbrain structure providing extensive 5-hydroxytryptamine (5-HT) innervation to the limbic forebrain. In parkinsonian rats, the basal firing of 5-HT neurons was increased, and STN HFS reduced it by more than 50%, providing support for a functional link between STN and DRN neurons (Temel et al., 2007). Regarding the cerebral cortex, STN HFS has been shown to activate antidromically the neurons of layer V/VI and dampen the cortical slow-wave oscillations (recorded by EEG and local field potentials from rats under deep anaesthesia), possibly by activating local excitatory and inhibitory cortical networks. Intracellular recordings showed that a small group (~16%) of layer V/VI neurons responded to STN HFS with an antidromic spike, whose frequency reflected that of DBS and with a latency of ~2 ms, while the remaining neurons responded with a reduction of membrane potential fluctuations (Li et al., 2007). These findings support the idea that cerebral cortex is involved in the mechanisms of action of STN HFS, as proposed by several studies in patients showing that this treatment 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). Antidromic activation of the cortex has also been reported in awake cataleptic rats during STN HFS (Dejean et al., 2009). Besides antidromic mechanism, however, STN HFS could act at cortical level also by the recently described direct subthalamocortical projection (Degos et al., 2009).

Molecular biology and metabolism

Molecular studies in 6-OHDA-lesioned rats have shown that STN HFS (2–4 h) induced the expression of the transcription factors c-fos, c-jun and Krox-24 (Schulte et al., 2006) in STN neurons and, at the same time, reduced the expression of cytochrome oxidase subunit I (COI) mRNA that normally is increased by DA depletion (Salin et al., 2002). Decrease of COI mRNA expression was also observed in the SNr after its increase triggered by DA lesion. Such reduction of COI mRNA in the STN and SNr after STN HFS is consistent with a reduction or normalization of neuron firing rate. Interestingly, COI mRNA levels in the cortex (layer V neurons), which were reduced by 6-OHDA lesion, could be normalized by STN HFS (Oueslati et al., 2007), further supporting an effect of STN manipulation at cortical level. Another marker of neuronal activity, glutamic acid decarboxylase (GAD) mRNA, was decreased in the EP, GP and SNr by prolonged (4 days) STN HFS, suggesting a reduced glutamatergic input from the STN to these GABAergic structures (Bacci et al., 2004; Benazzouz et al., 2004; Salin et al., 2002; Tai et al., 2003). Conversely, 10 days STN HFS in MPTP-treated monkeys resulted in an increased COI expression in the GPi, suggesting that longer period of STN stimulation would, on the contrary, increase GPi activity (Meissner et al., 2007). On the other hand, micro-dialysis experiments showed that STN HFS increased extracellular GABA in the SNr, which could arise from the concomitant stimulation of pallido-nigral fibres (Windels et al., 2005), suggesting a potential role of GABA originating from the GP in the inhibition of BG output structures during STN stimulation.

The metabolic effects of STN HFS have been studied by measuring 2-deoxyglucose (2-DG)

uptake in MPTP monkeys (Meissner et al., 2007). Such DA lesion induced a decrease of 2-DG accumulation in the STN that was reversed by 10 days STN HFS. Despite the significance of 2-DG uptake is still not clear in terms of excitatory or inhibitory influence and cellular elements involved, this study concluded that STN HFS could normalize the abnormal responses of BG structures to DA lesion resulting in STN hyperactivity.

Neuroprotective effects

STN HFS, applied 1 h per day, starting a week after 6-OHDA injection and during a period of 3 months, has been shown to enhance the survival of midbrain DAergic neurons in 6-OHDA-treated rats (Temel et al., 2006), and a similar work showed that continuous STN HFS (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 in MPTP-treated monkeys provided about 20% neuroprotection to DAergic cells (Wallace et al., 2007). Thus, although clinical findings reported that STN HFS failed to improve DA outflow in PD patients or increase the survival of DAergic cells (Hilker et al., 2003; Thobois et al., 2003), most of the studies in animal models with partial DA lesion are in agreement with an activation/preservation of the DAergic system by STN HFS. However, this effect is unlikely to participate to the therapeutic action in late stages of PD, when patients usually undergo HFS, due to the already extensive loss of DAergic neurons.

HFS of the STN is nowadays the main surgical treatment for PD, and thus it has received high attention by researchers. Overall, experimental data in PD models indicate that, while the activity of STN itself seems to be reduced by HFS, still the consequences of this treatment are much more complex than inhibition and, most importantly, they are widespread – directly or indirectly – to the other BG structures, to the thalamus and to the cerebral cortex (Gubellini et al., 2009). *In vitro* electrophysiological studies show that STN HFS interferes with the pacemaker-like activity of STN neurons resulting in short-term inhibition of firing discharge and, at long term, in the replacement of spontaneous firing activity by a stimulus-driven one. These evidences suggest 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.

Effects of manipulation of the STN on motor behaviour

Lesion, pharmacological and molecular STN inactivation in monkeys

STN lesions in intact monkeys were first reported to induce a characteristic transient hyper-kinetic syndrome called 'ballism' or 'hemiballism' (Whittier and Mettler, 1949). The first paper showing anti-parkinsonian effects of STN lesions in MPTP monkeys was published by Bergman and collaborators (Bergman et al., 1990), who showed that serious motor impairments induced by MPTP could be alleviated by STN lesions. The study was performed by means of general observation of gross motor behaviour, with no measure of controlled operant responses. This pioneer study was confirmed later (Aziz et al., 1991). In line with these reports, it was also shown that subthalamotomy performed in MPTP monkeys had a beneficial effect on certain motor deficits, but could also be detrimental by inducing hyperkinetic movements and hemiballism (Guridi et al., 1994, 1996; Wichmann et al., 1994).

In the hemiparkinsonian marmoset, it was also shown that unilateral STN lesion reversed the bias in head position and decreased latencies to initiate reaching on the contralateral side in the staircase grasping task. However, slight deficits in skilled

movements persisted (Henderson et al., 1998). Akinesia and bradykinesia were strongly ameliorated by discrete inactivation of the lateral part of the sensorimotor territory of STN performed with muscimol infusions (Baron et al., 2002).

More recently, another way of reducing STN activity in hemiparkinsonian monkeys has been developed using transfection with an adeno-associated virus containing the gene for GAD. Changing the glutamatergic phenotype into GABA of STN neurons allowed motor recovery into a certain extent and was thus considered as beneficial for the treatment of PD (Emborg et al., 2007).

All these beneficial effects of STN inactivation in parkinsonian monkeys are in line with the report showing that pharmacological blockade of STN by lidocaine or muscimol improves bradykinesia, limb tremor and rigidity in parkinsonian patients (Levy et al., 2001).

STN HFS in monkeys

Benazzouz and colleagues 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 (Benazzouz et al., 1993). This pioneer work was actually at the origin of the idea to apply STN HFS in PD patients. In the intact monkey, it was also shown that STN HFS could induce hyper-kinetic movements similar to the hemiballism observed after STN lesions (Beurrier et al., 1997). In contrast to what was described after STN lesions, STN HFS does not seem to induce hyper-kinetic movements when applied to MPTP monkeys and when compared to L-DOPA effects (Benazzouz et al., 1996).

Lesion, pharmacological and molecular STN inactivation in rats

In intact rats, unilateral lesion of the STN only produces transient hyper-kinetic movements of the contralateral paw. This behaviour has been quantified by measuring spontaneous circling behaviour (Kafetzopoulos and Papadopoulos, 1983). When the lesion is bilateral, this behavioural effect was rarely described. Only a trend to hyper-locomotion has been reported, as well as premature responses in the RT procedure illustrated in Fig. 2 (Baunez et al., 1995).

In rat models of PD, it was first shown that STN lesion alleviated the cataleptic state induced by a high dose of haloperidol (Zadow and Schmidt, 1994). When performed unilaterally, STN lesion can reduce circling behaviour induced by either a DA D2 receptor agonist or apomorphine in hemiparkinsonian rats (Anderson et al., 1992; Blandini et al., 1997; Burbaud et al., 1995). These were the first studies showing that STN lesion had a beneficial effect in alleviating gross motor deficits induced by DArgic depletion. In line with these beneficial effects of STN lesion on these types of motor behaviour, it was also shown that unilateral STN lesions could alleviate postural asymmetry induced by unilateral DA depletion (Phillips et al., 1998).

In order to measure the effects of bilateral STN lesions in a rat model of early PD, we have tested their effects in parkinsonian rats performing the SRT task described above. As shown in Fig. 3, bilateral lesions of the DA terminals in the dorsal striatum increased the number of delayed responses, as well as the mean RT for correct responses, characterizing an akinetic-like pattern of performance. Consecutive bilateral lesions of the STN alleviated this akinetic-like deficit, but the rats maintained a poor level of performance in the SRT task due to the appearance of a premature-responding deficit (Baunez et al., 1995). 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 behaviour. These results were confirmed by a similar study carried out with unilateral STN lesion (Phillips and Brown, 1999). In another study, it was also confirmed that STN

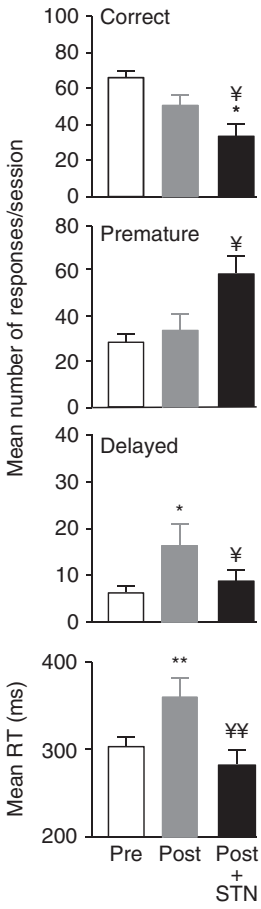

Fig. 3. Effects of STN lesions in a rat model of parkinsonism on the performance in the SRT task (Baunez et al., 1995). The performance is illustrated in terms of number of correct responses/100 trial session before surgery (Pre), after 6-OHDA lesion (Post) and after STN lesion consecutive to 6-OHDA lesion (post+STN). The dopaminergic depletion of the dorsal striatum induced an akinetic-like deficit characterized by an increased number of delayed responses (responses with a RT above 600 ms) and an overall increased RT for correct responses. Performing a bilateral lesion of the STN in these animals alleviated these two major deficits, but affected further the performance in terms of correct responses because of a dramatic premature-responding deficit. *,**, significantly different from pre-operative performance; ¥,¥¥: significantly different from post-operative performance (6-OHDA lesion effect), $p < 0.05$ and 0.0,1 respectively.

lesion alleviates some of the deficits induced by DA depletion, but induces side-effects and is unable to correct some deficits such as a paw reaching deficit assessed with a stair case (Henderson et al., 1999).

Other means of STN inactivation have been investigated for anti-parkinsonian therapy, notably addressing GABAergic transmission. The classic GABA agonist muscimol was shown to reduce circling behaviour induced by apomorphine and limb-use asymmetry in hemiparkinsonian rats (Mehta and Chesselet, 2005). The therapy by *GAD* gene transfection in the STN led to motor improvement in parkinsonian rats (Luo et al., 2002), so did GABAergic cell grafts into the STN (Mukhida et al., 2008).

Some of the beneficial effects observed after inactivation of the STN might be mediated via a specific system such as the 5-HT system. Indeed, the STN receives an important 5-HT innervation from the dorsal raphe (Parent and Hazrati, 1995b) and therefore affecting this transmission may result in behavioural changes, as those described after STN inactivation. It has been recently shown that targeting specifically 5-HT_{1A} receptors into the STN could alleviate L-DOPA-induced dyskinesia (Marin et al., 2009), confirming the possible critical influence of the 5-HT innervation to the STN in the functioning of the BG.

STN HFS in rats

The first study published on STN HFS in freely moving rats performing behavioural tasks used unilateral stimulation as well as unilateral SNc lesion. In this work we assessed both basic motor tasks such as haloperidol-induced catalepsy, apomorphine-induced circling behaviour, as well as a choice RT task (Darbaky et al., 2003). The parameters were set at 130 Hz, 60–70 μs pulse width and intensity set just below the threshold of hyperkinetic movements of the contralateral paw. We

showed that both the cataleptic state induced by haloperidol and the circling behaviour induced by apomorphine in unilateral DA-depleted rats could be alleviated by unilateral STN HFS. However, in a choice RT task, only a few animals remained able to perform the task after the DA depletion and the STN HFS did not help the severely impaired animals. Thus, in contrast to the spectacular effect of STN HFS in PD patients, the stimulation applied in the rat could not overcome the profound deficit preventing the animals to perform the task. Interestingly, however, for those able to perform the task, STN HFS alleviated the deficit expressed as a decreased ability to initiate a response towards the side contralateral to the DA lesion (Darbaky et al., 2003). Our conclusion 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 that will be developed in the next paragraph. Later the same year, another group showed that STN HFS had a beneficial effect on treadmill walking in parkinsonian rats (Chang et al., 2003) and reduced asymmetry when STN HFS was applied in hemiparkinsonian rats (Shi et al., 2004). We also showed that STN HFS could restore the use of the contralateral paw that was impaired after unilateral 6-OHDA lesion, but was not efficient to alleviate L-DOPA-induced dyskinesia (Gubellini et al., 2006), in line with a bilateral STN lesion study (Marin et al., 2004) and, possibly, because of the well-known effect of STN HFS itself in inducing dyskinesia (Boulet et al., 2006). When applied to intact rats, unilateral STN HFS induces contralateral circling behaviour that can be reduced by DA receptor antagonists (Bergmann et al., 2004).

The first study testing the effects of bilateral STN HFS was carried out in intact rats performing a RT task. STN HFS in that study decreased the premature responses depending on the stimulation 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 behaviour, there is consensus around a beneficial effect of STN HFS on parkinsonian motor deficits, although this treatment is not applied always in the same manner (unilateral vs. bilateral, monopolar vs. bipolar electrodes, individual adjusted parameters or not). However, the question of a possible detrimental effect, or at least a lack of effect on cognitive processes, has been raised by several studies and needs to be further investigated. The evidences gained from animal models (Darbaky et al., 2003; Temel et al., 2005) seem thus to confirm that STN HFS at parameters inducing beneficial effects on motor functions does not always correlate with beneficial cognitive effects, as reported in human patients (Perriol et al., 2006).

Effects of manipulation of the STN on cognition and motivation

When considering cortico-BG-thalamocortical connectivity as comprising five parallel loops (Alexander et al., 1986) (reviewed above), it becomes apparent that both GPi and STN are involved in each loop, including the associative and the limbic ones. These structures should not therefore be considered as contributing to motor behaviour only. Indeed, as illustrated in Fig. 4, 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 nucleus accumbens and the ventral pallidum, well-known for their involvement in motivational processes. These anatomical considerations lead us to investigate the involvement of the STN in non-motor behaviour.

STN lesion or STN HFS in monkeys

Only a limited number of groups study the effects of STN HFS in animals and none have published

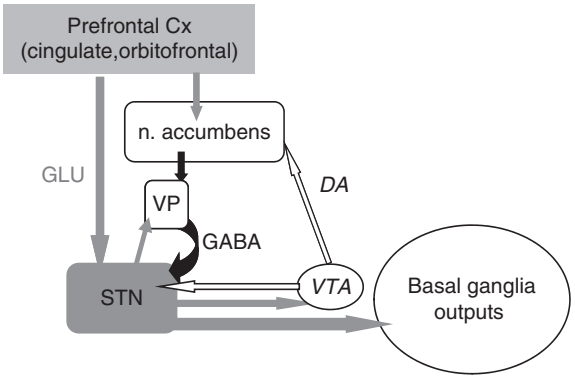

Fig. 4. The STN in the limbic loop. The STN receives direct inputs from the prefrontal cortex and indirectly connected with the nucleus accumbens via the ventral pallidum (VP). It receives inputs from the DA nuclei: ventral tegmental area (VTA) and substantia nigra pars compacta.

yet any study investigating its possible effects on cognitive processes in monkeys. The number of investigations focusing on cognitive processes in patients has increased in the recent years and might explain why there is little interest for these studies applied to non-human primates. However, it has been shown that STN neurons respond to reward (Darbaky et al., 2005), suggesting that STN manipulations may affect motivation.

STN lesion in rats

There are only a few studies dedicated to the involvement of STN in learning and memory processes. It has been shown that STN lesion does not seriously affect 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). In our study using a SRT task in 1995, we had suggested that premature responses could reflect an attentional impairment (Baunez et al., 1995). We have used the '5-choice serial RT task' in which the animals are trained to wait and detect a brief visual stimulus that can be presented in five possible various locations. The animals have to divide their attention between these five possible choices and then go and respond by a nose poke in the appropriate location to obtain a food reward in a food magazine and then initiate the next trial (see Fig. 5). Using this specific visual attentional task, we have studied the effects of STN lesions first, and then of STN lesions combined with a bilateral DA depletion in the dorsal striatum. We first showed that bilateral excitotoxic lesions of the STN-induced multiple independent deficits in the task, such as impaired accuracy suggestive of an attentional deficit; an increased level of premature responses suggestive of increased impulsivity; an increased level of perseverative responses towards the response locations and the magazine where the animals collect the food reward, suggestive of deficit in response control and an increased level of motivation for the reward (Baunez and Robbins, 1997). These results were the first to highlight the involvement of STN in cognitive functions. These results were replicated after blockade of the GABA receptors into the STN with muscimol (Baunez and Robbins, 1999b).

When lesioning the 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, most of the deficits were more motor related (omissions, increased latencies). Interestingly, when combining this 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, by lesioning the prefrontal cortex on one side and the STN on the other side, we have given the first evidence of a functional role for the hyper-direct pathway in the attentional and perseverative deficits observed in this attentional task (Chudasama et al., 2003). Further studies have confirmed the role of STN in impulse control. It was indeed shown that STN lesions prevent the animals to be

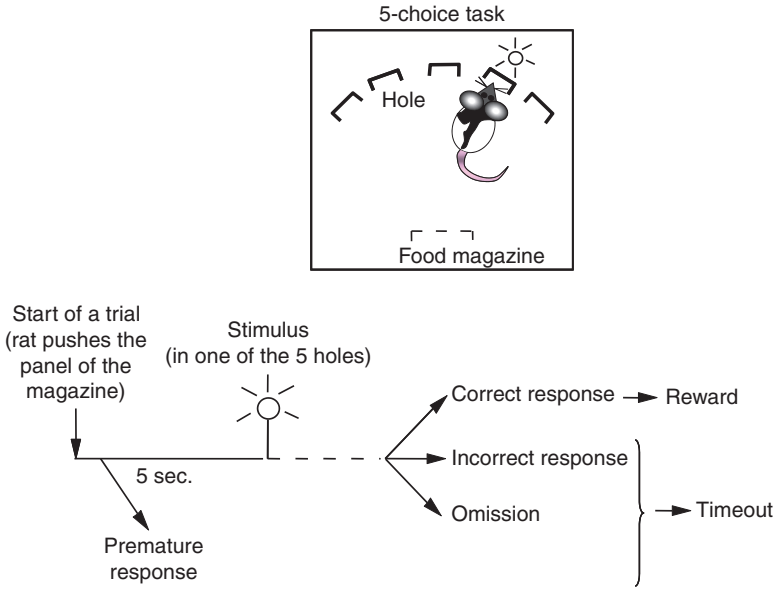

Fig. 5. The 5-choice serial reaction-time task (5-CSRTT): The rats initiate a trial by a nose poke in the food magazine. After a 5 s delay, a brief light (500 ms) is presented in one of the five holes. The rats have to detect and respond by a nose poke in the illuminated hole within 5 s to obtain a reward, 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 is recorded as a premature response and punished by a time-out (extinction of the house-light). The same punishment occurs if the rats respond in the wrong hole (incorrect response) or do not respond within 5 s (omission). After the first response has been given, additional nose pokes in the various holes are recorded as 'perseverative responses'. Detection of the rats' nose in the food magazine other than the first one after reward delivery are recorded as 'perseverative panel pushes' and characterize inappropriate visits to the magazine.

able to stop an ongoing action in a stop-signal RT task (Eagle et al., 2008). However, when tested in a behavioural task where the animals are given the choice between a small but immediate reward and a large but delayed reward, the STN-lesioned animals were able to overcome their impulsivity and wait for a bigger reward (Winstanley et al., 2005). This latter result was confirmed by another group (Uslaner and Robinson, 2006). These results suggest a specific role of STN in the control of inhibition that can be under the influence of the outcome (Eagle and Baunez, 2010).

STN HFS data in rats

We have 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 sometime induce an increased number of premature responses (Turle-Lorenzo et al., 2006). Temel and colleagues also reported this type of deficit in parkinsonian rats performing a choice RT task, together with increased RT and movement time (MT) (Temel et al., 2005). Interestingly, they have shown that bilateral STN HFS could alleviate the premature-responding deficit at lower current intensity (3 μA) than that reducing RT and MT (30 μA). As mentioned above, this study provides the evidence that cognitive and motor deficits may require a different threshold of HFS to be treated. In intact and parkinsonian rats, we have tested the effects of bilateral STN HFS and could therefore compare them to those induced by bilateral

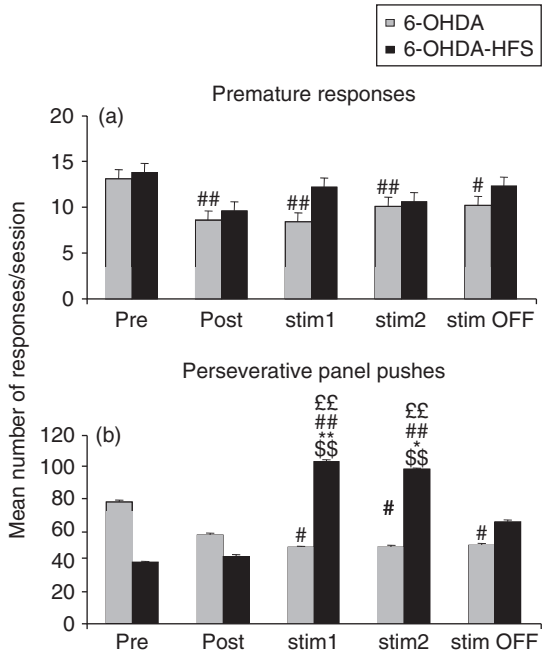

Fig. 6. Effects of bilateral high-frequency stimulation (HFS) of the STN in the 5-CSRTT (see Fig. 5) applied in 6-OHDA-lesioned rats (taken from Baunez et al., 2007). The performance in the 5-CSRTT is illustrated here for premature responses and perseverative responses into the food magazine (panel pushes) in the 6-OHDA-lesioned animals remaining OFF STN HFS (grey) and 6-OHDA-lesioned animals subjected to STN HFS (black) at the different stages of the experiment: during a block of 6 sessions before surgery (Pre), during a block of 6 sessions after surgery without stimulation (Post), during the first block of 6 sessions under STN HFS (stim 1), during the second block of 6 sessions under STN HFS (stim 2) and during a block of 6 sessions during which the stimulation was turned OFF (stim OFF). Vertical bar: SEM. *, **: $p < 0.05$ and $p < 0.01$, respectively, compared with sham group. #, ##: $p < 0.05$ and $p < 0.01$, respectively, compared with pre-operative performance. $,$$: $p < 0.05$ and $p < 0.01$, respectively, compared with 6-OHDA group. £: $p < 0.01$ compared with post-operative performance.

excitotoxic STN lesions in the visual attentional task described above. For both intact and parkinsonian animals, the effects of STN HFS were slightly different to those induced by STN lesions (Baunez et al., 2007). Accuracy of performance as well as latency to make a correct response was only transiently affected, while no effect on premature responses could be seen. Interestingly, the perseverative responses on both response location and reward magazine were found, in line with the lesion study. In parkinsonian rats, the subtle deficits recorded in the 5-choices RT task were neither 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 (Fig. 6) (Baunez et al., 2007).

These results are in line with recent studies focusing on the role of STN in motivational processes and suggest that inactivating the STN in parkinsonian animals should affect their motivational state.

We have first shown that bilateral STN lesion does not increase hunger or affect primary processes of motivation 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 these consummatory processes (Baunez et al., 2002, 2005; Lardeux and Baunez, 2008). When assessing motivation by measures of reactivity to stimuli predicting food, we found that STN lesions increase responses to these stimuli (Baunez et al., 2002). This result was further confirmed by another group (Uslaner et al., 2008). We also showed that STN lesion increases willingness to work on a lever to obtain food pellets and increases the score of preference for an environment previously associated with food. 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). When testing the effects of bilateral STN lesion on motivation for alcohol, we have further shown that it could also affect motivation in an opposite manner depending on the initial preference of the animals for the reward (Lardeux and Baunez, 2008). Very recently, we have shown that bilateral STN HFS reduces motivation for cocaine, while increasing that for food (Rouaud et al., 2010), in line with the results described after bilateral STN lesion (Baunez et al., 2005). Furthermore, electrophysiological recording of STN neurons in rats revealed that they can encode the value of the reward (Lardeux et al., 2009). It was shown that STN neurons can be categorized into sub-populations responding differently to reward. One sub-population responded exclusively to a cue predicting a 4% sucrose solution, but did not respond to the cue predicting the other reward (32% sucrose solution). The other sub-population responded to the cue predicting 32% sucrose, but not to the cue predicting 4%. In another study, we further showed that this dissociation also is observed when sucrose and cocaine are the two different rewards (Lardeux et al., 2008). Whether or not this encoding of the value of reward is dependent on the integrity of the DA system and could therefore be different in a rat model of PD remains to be elucidated.

Although there are no data available about the effects of STN manipulation on motivation in animal models of PD, these results that we have obtained in intact rats are in line with some clinical observations in PD patients after STN DBS, reporting craving for sweet food in some cases, or decreased addictive behaviour towards DAergic treatment (Knobel et al., 2008; Lim et al., 2009; Witjas et al., 2005).

In conclusion for this section on the STN, it has been shown that most of the effects observed were in line with a beneficial effect of STN inactivation for the treatment of motor symptoms in PD. The studies in rats have raised the issue of non-motor involvement of STN and lead to a better consideration of these aspects in clinical studies and patients' management: the current interest for motivational and emotional effects of STN DBS in PD patients reflects also the recent interest for these processes in animal models.

General conclusion

In conclusion, this review of the literature leads to the following comments:

At the cellular level, electrical stimulation of the GPi and the STN has a profound effect on the firing activity of their neurons. Rather than a mere inhibition of action potential discharge, HFS time-locks the activity of STN neurons at frequencies correlated to those of HFS. On the other hand, GPi stimulation seems also to exert an overall inhibitory effect. At neurophysiological level, it is now clear that the action of STN HFS spreads to surrounding brain structures that are directly or indirectly connected to this nucleus: the cortex, the striatum and other BG nuclei. Similarly, GPi HFS affects the activity of the striatum and the motor cortex activity. Regarding the GPi or STN inactivation by lesion procedures, too little experimental data are available to draw any consistent conclusion.

When investigating the motor behaviour, numerous studies carried out in animal models

have provided data supporting the role of GPi or STN as suitable targets for the treatment of parkinsonism. Almost all of these studies confirmed the beneficial effects of surgical interventions targeting GPi or STN on motor behaviour.

However, it is important to note that there are much more studies focusing on STN than on GPi or EP, possibly in line with the predominance of STN surgery in PD over pallidotomies or GPi DBS.. However, the possible cognitive and motivational side-effects observed after STN inactivation could lead to a revival of GPi as the target of choice. Although the clinical reports indicate only mild cognitive impairment after GPi manipulation, studies on cognitive and motivational processes in animals are needed. They could lead to a better profile of what should be investigated in these behavioural processes in patients.

In general, there is a poor investigation of behavioural consequences of HFS in either GPi or STN carried out in monkeys, possibly due to the fact that numerous clinical reports are published every year and might thus reduce the interest in proving behavioural efficacy of this surgical strategy in non-human primates. Most of the available studies using HFS in monkeys aimed at understanding the mechanisms of DBS. It would, however, be of great interest to also study behavioural effects in order to better understand the functional role of GPi and STN in the non-human primate, especially regarding non-motor behaviour. When it comes to cognitive and motivational processes, mainly rat data are available. These studies highlighted the integrative function of the STN, placing it at the interface between motivation and action. There was often a parallel to these findings in clinical observations of PD patients with STN DBS, 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) that are impossible to perform in the rat given the small size of the STN in this species.

A better knowledge of the possible consequences of GPi or STN inactivation in animals on various types of behaviour involving motor, cognitive and motivational processes was important for the treatment of PD patients and has lead to a more cautious attitude towards the criteria of selection for surgery. Indeed, with the increasing interest in cognitive and psychiatric consequences of STN DBS, the psychiatric examination of the patients has been taken more seriously in order to anticipate and avoid possible untoward effects of this treatment.

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Abbreviations

5-CSRTT	5-choice serial reaction-time task
5-HT	5-hydroxytriptamine or serotonin
6-OHDA	6-hydroxydopamine
BG	basal ganglia
DBS	deep brain stimulation
GPe/i	external/internal segment of the globus pallidus
HFS	high-frequency stimulation
L-DOPA	L-3,4-dihydroxyphenylalanine
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
PD	Parkinson's disease
RT	reaction time

SNc/r	substantia nigra pars compacta/ reticulata
SRT	simple reaction time
STN	subthalamic nucleus

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