REVIEW ARTICLE

The subthalamic nucleus in the context of movement disorders

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Summary

The subthalamic nucleus (STN) has been regarded as an important modulator of basal ganglia output. It receives its major afferents from the cerebral cortex, thalamus, globus pallidus externus and brainstem, and projects mainly to both segments of the globus pallidus, substantia nigra, striatum and brainstem. The STN is essentially composed of projection glutamatergic neurons. Lesions of the STN induce choreiform abnormal movements and ballism on the contralateral side of the body. In animal models of Parkinson’s disease this nucleus may be dysfunctional and neurons may fire in oscillatory patterns that can be closely related to tremor. Both STN lesions and high frequency stimulation ameliorate the major motor symptoms of parkinsonism in humans and animal models of Parkinson’s disease and reverse certain electrophysiological and metabolic consequences of dopamine depletion. These new findings have led to a renewed interest in the STN. The aim of the present article is to review briefly the major anatomical, pharmacological and physiological aspects of the STN, as well as its involvement in the pathophysiology and treatment of Parkinson’s disease.

Keywords: subthalamic nucleus; Parkinson’s disease; basal ganglia; deep brain stimulation; movement disorders

Abbreviations: AMPA = 2-aminomethyl-phenylacetic acid; BG = basal ganglia; CM = centromedian; EPSP = excitatory post-synaptic potential; GPe = globus pallidus externus; GPi = globus pallidus internus; HFS = high frequency stimulation; IPSP = inhibitory post-synaptic potential; mGluR = multiple glutamate receptors; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA = N-methyl-D-aspartate; Pf = parafascicular; PPN = pedunculopontine nucleus; SNc = substantia nigra compacta; SNr = substantia nigra reticulata; STN = subthalamic nucleus

Introduction

The subthalamic nucleus has been regarded as an important structure in modulation of activity of output basal ganglia structures and has been implied in the pathophysiology of Parkinson’s disease. Despite the current interest, little is known about its normal function in relation to movement. In the present study we review the anatomical, pharmacological and physiological attributes of the STN, with particular attention to its involvement in the pathophysiology of movement disorders and other neurological conditions.

Anatomy of the subthalamic nucleus

The subthalamic nucleus is a biconvex-shaped structure surrounded by dense bundles of myelinated fibres (Fig. 1) (Yelnik and Percheron, 1979). Its anterior and lateral limits are enclosed by fibres of the internal capsule that separate this nucleus laterally from the globus pallidus. Rostromedially, the STN abuts on the nucleus of the Fields of Forel, the Field H of Forel and the posterior lateral hypothalamic area. Posteroomedially it is adjacent to the red nucleus. Its ventral limits are the cerebral peduncle and the substantia nigra (ventrolaterally). Dorsally the STN is limited by a portion of the fasciculus lenticularis and the zona incerta, which separate this nucleus from the ventral thalamus (Schaltenbrand and Wahren, 1977; Yelnik and Percheron, 1979; Williams and Warwick, 1980; Chang et al., 1983; Kita et al., 1983; Parent and Hazrati, 1995).
Several fibre tracts course near the borders of the STN. The subthalamic fasciculus consists of fibres that interconnect the STN and globus pallidus. This fibre bundle arises from the inferolateral border of the STN and crosses the internal capsule in its trajectory.

The ansa lenticularis contains fibres from the globus pallidus internus (GPi) that project towards the thalamus. It originates mainly from the lateral portion of the GPi coursing in a medial, ventral and rostral direction, sweeping anteriorly around the posterior limb of the internal capsule. Thereafter, these fibres course posteriorly to enter the H Field of Forel.

The lenticular fasciculus also contains pallidothalamic fibres and is designated H2 Field of Forel. This tract arises from the medial aspect of the GPi, perforates the internal capsule, and forms a bundle ventral to the zona incerta. Although some fibres from the lenticular fasciculus may be found dorsal to the STN, most of this tract courses rostral to the nucleus. In the H Field of Forel, the lenticular fasciculus joins the ansa lenticularis and fibres that come from the superior cerebellar peduncle and brainstem, forming the thalamic fasciculus (H1 Field of Forel) (Parent et al., 2000).

The view of the ansa lenticularis and lenticular fasciculus as distinct anatomic pathways has been challenged by recent papers (Baron et al., 2001).

Dopaminergic nigrostriatal fibres leave the dorsal and medial aspects of the substantia nigra compacta and course medially and dorsally in relation to the STN (through the medial forebrain bundle), reaching the H Field of Forel from where they ascend to terminally arborize in the striatum. This system gives rise to fibres that innervate all major structures of the basal ganglia, including the STN and the globus pallidus (Parent et al., 2000). Fibre tracts that lie posterior to the STN include the medial lemniscus, spinothalamic tract, trigeminothalamic tract and reticulothalamic tract (Butler and Hodos, 1996).

The average number of neurons in each STN nucleus varies from species to species and has been estimated to be ~25 000 in rats, 35 000 in marmosets, 155 000 in macaques, 230 000 in baboons and 560 000 in humans (Oorschot, 1996; Hardman et al., 1997, 2002). The density of STN neurons (number of neurons per volume of tissue) in rodents, primates and humans does not vary significantly, as the volume of this nucleus progressively increases among species. The volume of the STN is ~0.8 mm³ in rats, 2.7 mm³ in marmosets, 34 mm³ in macaques, 50 mm³ in baboons and 240 mm³ in humans (Hardman et al., 2002). The relationship between the volume of the STN and the total volume of the brain in non-human primates and humans is proportionally similar (Carpenter, 1982).

The vascular supply to the STN is from perforating branches of the anterior choroidal artery (pedunculo-subthalamic arteries), posterior communicating artery (pedunculosubthalamic arteries and branches of the thalamic polar artery) and posteromedial choroidal arteries (lateral mesencephalosubthalamic arteries). The former two arteries are branches of the internal carotid artery, whereas the latter vessels are part of the posterior circulation. The contribution of each of these vessels to the arterial supply of the STN is variable and their vascular territories intermingle (Percheron, 1982). The antiparkinsonian effects of anterior choroidal artery ligation, proposed in the past for the treatment of Parkinson’s disease (Cooper, 1953), might have been related, at least in part, to the infarction of the STN and related structures.

**Histology of the subthalamic nucleus**

The subthalamic nucleus is populated mainly by projection neurons (Rafols and Fox, 1976; Iwahori, 1978; Chang et al., 1983, 1984; Afsharpour, 1985a). Their somata (10–25 μm in rodents and 35–40 μm in primates) are abundant with mitochondria, lysosomes, microtubules, neurofilaments, ribosomes and Golgi apparatus, but not endoplasmatic reticulum (Rafols and Fox, 1976; Chang et al., 1983). The nucleus and nucleoplasm are pale, containing dispersed chromatin and an invaginated nuclear envelope (Rafols and Fox, 1976; Chang et al., 1983). As the STN is a densely populated nucleus,
extensive membrane apposition between the cell bodies, dendrites, and initial segments of the axons is observed (Chang et al., 1983).

STN neurons have two to eight dendritic trunks that give rise to thinner dendrites, whose fields are usually oval with their long axis parallel to the long axis of the nucleus, extending up to 750 μm in primates (Rafols and Fox, 1976; Yelnik and Percheron, 1979; Afsharpour, 1985a; Sato et al., 2000a). In rodents, secondary dendrites bifurcate at distances between 18 and 100 μm from the cell body and may extend up to 500 μm from the point of branching (Afsharpour, 1985a). The dendritic field of a single STN neuron can cover up to one-half of the nucleus in rats (Kita et al., 1983). The majority of STN dendrites and some portions of the soma are sparsely covered with spines (Rafols and Fox, 1976; Chang et al., 1983; Sato et al., 2000a). In rodents, two major types of synaptic terminals have been described on STN dendrites: a small type, which forms asymmetrical synapses and contains round vesicles (possibly glutamatergic) and a larger type, which forms symmetrical synaptic contacts and contains round and flattened vesicles (possibly GABAergic) (Chang et al., 1983).

In primates, distinct types of axonal branching patterns have recently been described in STN neurons, projecting, respectively, to (i) globus pallidus externus (GPe), GPi and substantia nigra reticulata (SNr) (21.3%), (ii) GPe and SNr (2.7%), (iii) GPe and GPi (48%), and (iv) GPe only (10.7%). The remaining projecting fibres course towards the striatum, but their terminals have not been fully characterized (17.3%) (Sato et al., 2000a). Axons that provide collaterals to the pallidum and substantia nigra bifurcate into rostral and caudal branches, whereas axons that provide collaterals only to the pallidum or to the striatum have a single branch that courses rostrally and dorsally and subsequently bifurcates (Sato et al., 2000a).

**Embryology of the STN**

The embryological diencephalic wall is divided into five zones during development: The epithalamic, the dorsal thalamus, the ventral thalamus and the hypothalamus sensu lato, which is further subdivided in hypothalamus sensu strictu and subthalamus, which will ultimately originate the subthalamic nucleus (Kuhlenbeck, 1948; Cooper, 1950; Marchand, 1987; Muller and O’Rahilly, 1988). In rodents, a germinative zone lying caudally along the dorsal aspect of the mammillary recess is responsible for the formation of the neurons of the subthalamic nucleus (Marchand, 1987). In humans, the subthalamic nucleus is derived from the proliferative epithelium of the marginal layer of the thalamus, and is initially seen as part of the intermediate layer around 33–35 days of gestational age (Muller and O’Rahilly, 1988). At ~44–48 days of gestational age, the STN can be seen as a condensation of cells in the periphery of the intermediate layer of the subthalamus, close to the mesencephalon and adjacent to the mammillary body (Muller and O’Rahilly, 1990). Between 48 and 51 days, the nucleus assumes its characteristic lens-shaped appearance (Lemire et al., 1975). As observed in other cerebral structures, from birth to 16 weeks after birth, the number of synapses in the STN of non-human primates declines by ~45% (Fisher et al., 1987).

**Intrinsic organization of the STN**

The basal ganglia have been subdivided into three functional units (Alexander et al., 1990; Parent and Hazrati, 1993; Parent and Hazrati, 1995; Joel and Weiner, 1997). Motor, associative and limbic cortical regions innervate, respectively, motor, associative and limbic regions of the striatum, pallidum and SNr. The motor circuit comprises: (i) motor cortical areas (primary motor cortex, supplementary motor cortex, pre-motor cortex, and portions of the somatosensory dorsal parietal cortex); (ii) the dorsolateral portion of the post-commissural putamen and a small rim of the head of the caudate; and (iii) the lateral two-thirds of the globus pallidus (GPe and GPi) and a small portion of the substantia nigra. The associative circuit is composed of (i) associative cortical regions (i.e. the dorsolateral and ventrolateral pre-frontal cortices, portions of the intraparietal sulcus, the border of the superior temporal sulcus), (ii) most of the caudate nucleus and the putamen rostral to the anterior commissure and (iii) the dorsal aspect of the medial third of the globus pallidus (GPe and GPi) and most of the substantia nigra. The limbic circuit is composed of (i) limbic cortical afferents (i.e. orbitofrontal cortical regions and the anterior cingulate gyrus), (ii) the nucleus accumbens and the most rostral portions of the striatum and (iii) the subcommissural ventral pallidum, small limbic regions in the ventral portion of the medial third of the globus pallidus (GPe and GPi), the medial tip of the substantia nigra, and the ventral tegmental area.

This distinct functional subdivision has also been applied to the STN. The STN is subdivided in two rostral thirds and a caudal third. Furthermore, the two rostral thirds are subdivided into medial (medial third) and lateral portions (lateral two-thirds).

The medial portion of the rostral two-thirds is thought to comprise the limbic and part of the associative territories. The ventral aspect of the lateral portion of the rostral two-thirds composes the other portion of the associative territory. The dorsal aspect of the lateral portion of the rostral two-thirds and the caudal third of the nucleus are related to motor circuits (Fig. 2) (Parent and Hazrati, 1995; Shink et al., 1996; Joel and Weiner, 1997).

**Subthalamic nucleus afferents**

**Cortico-subthalamic projections**

In primates, most of the cortical afferents to the STN arise from the primary motor cortex, supplementary motor area (SMA), pre-SMA, and the dorsal and ventral pre-motor
cortices (respectively PMd and PMv) (Nambu et al., 1996, 1997, 2002). These projections innervate predominantly the dorsal aspects of the nucleus and are integral components in the motor loops of the basal ganglia. The ventromedial portion of the STN receives afferents from the frontal eye field (area 8) and the supplementary frontal eye field (within area 9), and is involved in circuits related to eye movements (Matsumura et al., 1992; Stanton et al., 1988). In rodents, prelimbic-medial orbital areas of the prefrontal cortex project to the medial STN as part of the limbic loop (Groenewegen and Berendse, 1990). Additional projections from the cingulate cortex, somatosensory cortex, and insular cortex have been described in rodents and primates but their functional role is still unknown (Kunzle, 1977, 1978; Monakow et al., 1978; Carpenter et al., 1981b; Kitai and Deniau, 1981; Afsharpoor, 1985b; Jurgens, 1984; Canteras et al., 1990; Rinivik and Ottersen, 1993; Takada et al., 2001).

A complex and controversial intrinsic pattern of somatotopy has recently been reported in the STN (Monakow et al., 1978; Nambu et al., 1996, 1997, 2002). Former studies (Monakow et al., 1978) have described the somatotopic representation of the leg, arm and orofacial structures in the medial, lateral and dorsolateral portions of the STN, whereas recent reports have described multiple homunculi within the nucleus (Nambu et al., 1996, 1997). Primary motor cortex fibres related to the leg, arm and face are represented from medial to lateral in the lateral portion of the STN, whereas the medial portion of the nucleus receives fibres from the SMA, PMd and PMv in an inverse somatotopic distribution (leg, arm and face, respectively, represented from medial to lateral) (Nambu et al., 1996, 1997, 2002).

Cortical afferents from the primary motor cortex to the STN in rodents and cats originate mainly in layer V and are composed of collaterals of the pyramidal tract or cortical fibres that also innervate the striatum, although the former are more prevalent (Kitai and Deniau, 1981; Giuffrida et al., 1985). These pathways utilize glutamate as their neurotransmitter and their terminals make contact with small dendrites in the STN (Fig. 3) (Romansky et al., 1979; Morizumi et al., 1987).

**Pallido-subthalamic projections**

The external pallidal projection to the STN comprises one of its major afferents. Virtually the entire nucleus receives pallidal fibres, which course in a mediolateral and rostrocaudal direction (Parent and Hazrati, 1995). The topographic and somatotopic distribution of these afferents varies from species to species. In rodents, the lateral portions of the pallidum innervates the lateral STN, whereas the medial parts of the STN are innervated by the medial and ventral pallidum (Parent and Hazrati, 1995). In primates, a more complex topographic distribution of fibres has been reported. The rostral GPe (associative) innervates the medial two-thirds of the rostral STN, the central portion of the middle STN, and to a lesser extent the medial third of the middle STN. The central GPe (associative dorsomedially and sensorimotor ventrolaterally) projects to the lateral, caudal and, to a lesser extent, the central part of the rostral two-thirds of the STN. The ventral portion of the central GPe and the caudal GPe innervate the lateral and caudal STN (Carpenter et al., 1981a; Shink et al., 1996; Joel and Weiner, 1997). In summary, although motor and limbic portions of the GPe innervate their corresponding counterparts in the STN, it has been suggested that associative pallidal afferents innervate the associative portion of the STN as well as the motor territory, providing evidence for open circuits (that do not innervate their respective counterparts) in the tripartite model of functioning of the basal ganglia (Joel and Weiner, 1997; Parent and Cicchetti, 1998).

In primates, distinct GPe projection neurons have been identified. Of the GPe neurons 13.2% send projections to the GPi, STN and SNr, 18.4% only to the GPi and STN, and 52.6% only to the STN and SNr (Sato et al., 2000b). Pallidal terminals contact principally the proximal dendrites and cell bodies of STN neurons, although distal dendrites are also innervated (Parent and Hazrati, 1995). GABA is the main neurotransmitter in this pathway, which comprises the major inhibitory projection to the STN (Fig. 3) (Fonnum et al., 1978; Oertel and Mugnaini, 1984; Smith et al., 1987, 1990a; Smith and Parent, 1988).

**Thalamo-subthalamic projections**

The main projections from the thalamus to the STN originate in the parafascicular (PF) and centromedian nuclei (CM) (Sugimoto and Hattori, 1983; Sugimoto et al., 1983; Sadikot et al., 1992; Feger et al., 1994, 1997). In primates, the Pf nucleus is the predominant thalamic source of input to the STN, while it receives only a small number of centromedian fibres (Sadikot et al., 1992). In rodents, the Pf and CM form an undifferentiated complex.
A mediolateral topographic distribution of Pf-STN fibres has been described in rodents (Feger et al., 1994). In primates, however, Pf projects to the medial third of the rostral STN, whereas the CM projects to the dorsolateral motor territory of the nucleus (Sadikot et al., 1992). According to the intrinsic organization of the STN, Pf projections innervate the associative and limbic territories, whereas the CM nucleus projects to the sensorimotor territory (Parent and Hazrati, 1995).

The axonal terminals of the thalamic afferents are glutamatergic and contact mainly the dendrites of STN cells (Scatton and Lehmann, 1982; Nieoullon et al., 1985; Mouroux and Feger, 1993).

**Brainstem afferents to the STN**

The STN receives direct projections from the substantia nigra compacta in rodents, non-human primates and humans (Brown et al., 1979; Lavoie et al., 1989; François et al., 2000). The major neurotransmitter in this pathway is dopamine, which modulates the activity of glutamatergic cortical and GABAergic pallidal afferents to the subthalamic nucleus. Dopaminergic terminals contact mainly the neck of dendritic spines in the STN (Fig. 3).

The pedunculopontine nucleus (PPN) and laterodorsal tegmental nuclei send cholinergic inputs to the STN in rodents, contacting mostly dendrites (Gerfen et al., 1982; Jackson and Crossman, 1983; Scarnati et al., 1987; Lee et al., 1988; Lavoie and Parent, 1994). The non-cholinergic components of the PPN also project to the STN (Rye et al., 1987; Mesulam et al., 1992).

Another source of afferent innervation to the STN in rodents is the dorsal raphe nucleus (mainly its rostral section) (Woolf and Butcher, 1986; Canteras et al., 1990). This serotoninergic pathway may also be involved in the modulation of STN activity.
In addition to the above-mentioned projections, several other regions provide minor innervation to the STN in rodents, such as the reticular nucleus of the thalamus, the zona incerta, the locus coeruleus, the hypothalamus, the amygdala, the bed nucleus of the stria terminalis, the parabrachial nuclear complex and the dorsolateral tegmental nucleus (Canteras et al., 1990). Little is known about their organization and role in STN physiology.

**Subthalamic nucleus efferents**

**Subthalamo-pallidal projections**
The major efferent projections from the STN are directed to both segments of the globus pallidus (GPe and GPi/entopeduncular nucleus) in primates and rodents. STN fibres enter the pallidum through its posterior portion, coursing in a caudorostral direction (Smith et al., 1990b; Parent and Hazrati, 1995; Feger et al., 1997). In both segments of the pallidum, STN projections are uniformly arborized, affecting an extensive number of cells (Hazrati and Parent, 1992; Fujimoto and Kita, 1993). In non-human primates, STN fibres are distributed in elongated caudorostral pallidal bands that are parallel to the medullary laminae, obeying the dendritic fields of pallidal cells (Carpenter et al., 1981a, b; Smith et al., 1990b). Terminals within this pathway are glutamatergic and innervate mostly the dendritic shafts of pallidal neurons. STN projections to both segments of the globus pallidus obey a point-to-point distribution. The medial part of the rostral two-thirds of the STN projects primarily to the rostral GPe, ventral pallidum, and rostroventromedial portions of the GPi (associative and limbic territories). The ventral part of the lateral two-thirds of the rostral two-thirds of the STN project primarily to the dorsomedial third of GPe and GPi (associative territory). The dorsal two-thirds of this same STN region project to the ventrolateral GPe and GPi (motor territory). The caudal STN projects predominantly to the motor territory of the GPe and GPi, except for a small portion of the ventromedial aspect of this STN region, which projects to the associative pallidum (Parent and Hazrati, 1995; Shink et al., 1996; Joel and Weiner, 1997).

**Subthalamo-nigral projections**
The subthalamic nucleus innervates both components of the substantia nigra in rodents and non-human primates: the pars reticulata (SNr) and the pars compacta (SNC). Fibres from the STN enter the nigra mostly through its ventromedial region, spreading laterally in a rostrocaudal direction (Smith et al., 1990b; Parent and Hazrati, 1995). Although most of these fibres innervate the pars reticulata, some axons ascend and reach the pars compacta, comprising one of the mechanisms responsible for the regulation of dopamine release (Groenewegen and Berendse, 1990; Smith et al., 1990b; Parent and Hazrati, 1995). STN-nigral projections have their origin mostly in the ventromedial portion of the subthalamic nucleus in non-human primates (Parent and Smith, 1987). Once in the nigra, STN axons arborize and give rise to several local collaterals, which are thinner than the ones that project to the pallidum (Sato et al., 2000a). In rodents and felines, their terminal boutons contain glutamate vesicles and innervate mainly dendritic shafts in nigral cells (Chang et al., 1984; Kita and Kitai, 1987; Rinvik and Ottersen, 1993).

**Subthalamo-striatal projections**
The subthalamic nucleus sends scant projections to the striatum in rodents and non-human primates (Kita and Kitai, 1987; Smith et al., 1990b). In non-human primates, ventromedial associative and limbic regions of the STN innervate mostly the caudate, whereas dorsolateral motor portions of this nucleus innervate mostly the putamen (Parent and Smith, 1987). Contrasting with the efferents to the pallidum and nigra, STN projections to the striatum are poorly branched and provide generally en passant excitatory influence over striatal cells (Parent and Hazrati, 1995).

**Additional efferent projections**
Aside from the main efferent projections described above, the STN also send projections to the PPN and ventral tegmental area in rodents and non-human primates, through which it modulates their activity (Jackson and Crossman, 1981; Granata and Kitai, 1989; Smith et al., 1990b; Parent and Hazrati, 1995). The activation of the PPN increases activity in the nucleus reticularis gigantocellularis, which modulates part of the motor activity over the spinal cord (mostly spinal interneurons) through the reticulospinal tract (Pahapill and Lozano, 2000).

**Pharmacology of the subthalamic nucleus**

**Glutamate**
Excitatory amino acids provide the main excitatory drive to the STN. Although N-methyl-D-aspartate (NMDA), 2-amino-3-methyl-phenylacetatic acid (AMPA) and metabotropic receptors have been described in STN neurons, the role played by each particular subtype is disputed. In slices, the application of both NMDA and non-NMDA glutamatergic agents evoke more pronounced responses (Shen and Johnson, 2000). Indeed, AMPA receptors are enriched in the STN compared with NMDA receptors (Klockgether et al., 1991). Nevertheless, internal capsule stimulation-evoked excitatory post-synaptic potentials (EPSPs) are significantly blocked by NMDA antagonists and the topical application of these agents in the STN significantly decreases its metabolic activity (Nakanishi et al., 1988; Blandini et al., 2001). As in other cerebral structures, however, the activation of gated NMDA receptors is favoured in a more depolarized state, which in the STN is in part achieved through the activation of metabo-
tropic receptors (mGluR). Recent electrophysiological studies suggest that mGluR5 is the main subtype involved in mediating post-synaptic depolarization, excitation and potentiation of NMDA-evoked currents, although mGluR1 receptors and group III mGluR receptors also seem to play a role in the physiology of the STN (Awad et al., 2000; Awad-Granco and Conn, 2001). While the complexity of glutamate signalling and post-synaptic potentiation is not yet fully elucidated, it is clear that a combination of multiple glutamate receptor subtypes mediates a complex signalling pathway in the STN (Bevan and Wilson, 1999; Awad et al., 2000; Awad-Granco and Conn, 2001).

GABA
GABA has a major role in several aspects of the STN physiology, modulating its firing rate, pattern of discharges and bursting activity. The topical application of GABAergic agonists in the STN inhibits neuronal activity, whereas the reverse is true for GABAergic antagonists (Rouzaire-Dubois et al., 1980). The impact of GABAergic transmission in the STN is related to the initial membrane potential of the cells, which is strongly dictated by pallidal afferents (Bevan and Wilson, 1999; Bevan et al., 2000, 2002a, b).

GABAergic activity within the STN occurs mainly through the activation of post-synaptic GABA_A receptors, although recent evidence has shown that GABA_B also plays a role in its physiology (Bevan et al., 2000; Shen and Johnson, 2001; Urbain et al., 2002). GABA_A agonists reduce both glutamate EPSPs and GABA_A IPSPs, ultimately decreasing the firing rate in STN neurons (Shen and Johnson, 2001; Urbain et al., 2002). Although minor post-synaptic activity has been described, most GABA_B effects are pre-synaptic (Shen and Johnson, 2001).

Dopamine
Several studies have addressed the effects of both systemic and topical administration of dopaminergic agonists on STN activity, presenting sometimes contradictory results (Campbell et al., 1985; Mintz et al., 1986; Kreiss et al., 1996; Hassani et al., 1997; Kreiss et al., 1997; Hassani and Feger, 1999; Shen and Johnson, 2000; Ni et al., 2001).

It has generally been accepted that STN neurons express mRNA encoding dopamine D5 receptors, but not D1 and D2, which are present in pre-synaptic terminal afferents (Bouthenet et al., 1991; Mansour et al., 1991, 1992; Svenningsson and Le Moine, 2002). Cells in the pre-frontal cortex express both D1 and D2 mRNA, whereas globus pallidus neurons contain only D2 mRNA in rodents (Mansour et al., 1991, 1992; Hassani and Feger, 1999). In slices, the application of dopamine reduces both glutamatergic EPSPs and GABAergic inhibitory post-synaptic potentials (IPSPs) in the STN, in agreement with studies that show that dopamine has a depressive effect on neuronal excitability (Hassani and Feger, 1999; Shen and Johnson, 2000). Nevertheless, the most prominent effects on the IPSPs account for a final excitatory dopaminergic activity in the STN (Shen, 2000).

Studies in which the topical application of dopaminergic agonists in the STN was performed revealed different results. While some authors advocate that dopaminergic agonists exert an excitatory effect, particularly through the activation of D1 receptors (Mintz et al., 1986; Kreiss et al., 1996), others state that D1, D2 and non-specific agonists (particularly apomorphine) decrease STN activity (Campbell et al., 1985; Hassani and Feger, 1999).

In normal rodents, it is reported that the systemic administration of apomorphine increases STN activity, although the systemic effects of selective agonists are not so clear-cut. In general, it seems that D1 agonists increase STN activity, but only when D2 receptors are co-activated, whereas D2 agonists do not exert significant effects (Kreiss et al., 1997; Ni et al., 2001). As most of the structures that give rise to STN afferents are also modulated by dopamine, it is clear that the systemic administration of dopaminergic agents is linked to a complex cascade of responses and, so far, the exact role played by each structure and specific receptors is uncertain.

Serotonin/acetylcholine and miscellaneous
In slice preparations, serotonin increases the spontaneous activity in STN neurons (Flores et al., 1995; Martinez-Price and Geyer, 2002). The topical administration of serotonergic agonists in rodents increases locomotor activity, possibly through 5-hydroxytryptamine (serotonin) (5HT1B) receptors (Martinez-Price and Geyer, 2002).

In rodents, cholinergic agonists applied topically excite STN neurons (Feger et al., 1979). Application of muscarinic agonists in slices induces reduction in the amplitude of both EPSPs and IPSPs in the STN, particularly through M3 receptors (Flores et al., 1996; Shen and Johnson, 2000). As the effects in the latter potentials are higher, the end result is a final excitation that provides a subsequent release of glutamate from STN neurons (Rosales et al., 1994; Shen and Johnson, 2000). This effect has been suggested as one of the possible mechanisms for the antiparkinsonian effects of anticholinergic agents (Feger et al., 1979; Flores et al., 1996; Shen and Johnson, 2000).

In the STN, opioids inhibit both glutamate and GABA activity through μ and δ pre-synaptic receptors (Shen and Johnson, 2002).

Physiology of the STN
Physiological properties of STN cells
Findings from recordings of neuronal activity in the STN vary according to the technique employed, the general conditions of the experiments, and type of anaesthesia utilized.
It is estimated that in vivo 55–65% of the STN neurons fire irregularly, whereas 15–25% fire regularly and 15–50% present bursting activity in non-human primates (Wichmann et al., 1994a). The predominant pattern of activity in a single STN cell is mainly dictated by its initial membrane potential. Tonic firing is evoked with neuronal potentials around −35 to −50 mV, whereas bursting activity requires a more hyperpolarized condition, with the membrane potential around −40 to −60 mV. Below −60 mV neurons usually become silent and above −30 mV, activity increases in frequency and decreases in amplitude until its complete cessation (Beurrier et al., 1999; Bevan and Wilson, 1999; Bevan et al., 2000, 2002a).

The average firing rate of STN neurons is 13–18 Hz in normal rats and 18–25 Hz in non-human primates (Georgopoulos et al., 1983; DeLong et al., 1985; Matsumura et al., 1992; Fujimoto and Kita, 1993; Bergman et al., 1994; Wichmann et al., 1994a; Overton et al., 1995; Hassani et al., 1996, 1997; Kreiss et al., 1996, 1997; Beurrier et al., 1999; Urbain et al., 2000).

Oscillatory neuronal cycle in the STN
Neuronal oscillatory cycles usually consist of a slow depolarization, an action potential and a subsequent after-hyperpolarization (AHP) (Bevan and Wilson, 1999; Beurrier et al., 2000). In the STN, slow depolarization is evoked through tetrodotoxin (TTX)-sensitive sodium currents (voltage dependent), cationic currents, or low threshold calcium currents (mostly in the case of bursting activity), which are activated when the membrane potential of the cells is slightly more negative than the usual resting state. These events result in the entry of sodium and calcium into the cells, culminating with the generation of action potentials. Thereafter, in addition to usual hyperpolarization mechanisms, oscillatory cells are characterized by the presence of calcium-dependent potassium channels that, once activated, lead to a more hyperpolarized state, evoking the so-called after-hyperpolarized potentials (AHP). This negative potential promotes the activation of new slow depolarization currents and a subsequent new cycle (Bevan and Wilson, 1999; Beurrier et al., 2000).

Calcium and bursting activity
Aside from the regular oscillatory activity, STN neurons can also generate broad plateau potentials and bursting activity. These events are dependent on the activation of multiple calcium channels, as well as calcium-dependent potassium channels. As for regular oscillations, in order for a neuron to burst, the membrane potential has also to be more negative than in the resting state. In fact, thresholds for rebound oscillations and burst firing are similar to the equilibrium potential of GABA (Bevan and Wilson, 1999; Bevan et al., 2000). When the membrane potential is approximately −50 to −75 mV, STN cells submitted to depolarizing currents develop plateau potentials dependent on calcium channels (Beurrier et al., 1999). Units that do not develop plateaus generally do not present bursting activity.

In rats, low threshold calcium currents are generated through the activation of T-type calcium channels, located mostly in STN dendrites (Song et al., 2000). When the cells reach a more depolarized state, high threshold calcium channels (N, L, Q, R types) located in both dendrites and soma are activated (Song et al., 2000). Once high concentrations of intracellular calcium are achieved, plateau potentials are produced. Thereafter, action potentials and bursting activity are generated and calcium-dependent potassium channels are subsequently activated, leading the cells back to a hyperpolarized state, which culminates with the beginning of a new cycle (Beurrier et al., 1999).

Excitatory potentials and depolarization
In rodents and non-human primates, almost all STN cells respond to cortical stimulation, usually with triphasic potentials (positive, negative and positive) that are followed by long hyperpolarizations (Kitai and Deniau, 1981; Fujimoto and Kita, 1993; Nambu et al., 2000).

As latency for the first peak in triphasic potentials is ~2 ms, it has been suggested that this element is directly related to the activation of cortico-subthalamic pathways in rats and non-human primates (Fujimoto and Kita, 1993; Nambu et al., 2000). Thereafter, the subsequent orthodromic and/or antidromic activation of GPe neurons generates the inhibitory component that follows. Concomitant with the cortico-STN excitation, cortico-striatal and striatal-GPe pathways are also activated, culminating with disinhibition of the STN (Fujimoto and Kita, 1993; Feger et al., 1997; Nambu et al., 2000). This phenomenon seems to be responsible for the second excitatory peak, which takes place 15 ms after cortical stimulation (Fujimoto and Kita, 1993; Nambu et al., 2000).

Corroborating these observations, lesions of the globus pallidus (i) do not interfere with the first peak of STN excitatory responses, (ii) substantially decrease the inhibitory component of the responses and (iii) increase the second excitatory peak (Ryan and Clark, 1992; Ryan et al., 1992; Ryan and Sanders, 1993). Striatal lesions induce the opposite effects, although of lesser magnitude (Ryan and Clark, 1992; Ryan et al., 1992; Ryan and Sanders, 1993).

Cortico-STN-pallidal connections bypass the striatum, conveying excitatory input directly to the STN and pallidum. The term ‘hyperdirect pathway’ has been proposed for this pathway (Nambu et al., 1996; Nambu et al., 2002).

A second major source of excitatory input to the STN is the Pf thalamic nucleus. Stimulation of the parafascicular-STN projection also evokes a triphasic response. The mechanisms for the development of each component of the response are similar to those described for the cortico-STN pathway (Mouroux et al., 1995; Feger et al., 1997; Mouroux et al., 1997). Lesions of the Pf nucleus, as well as its pharmacological inhibition, lead to a reduced excitatory response in the ipsilateral STN (Mouroux et al., 1995; Feger et al., 1997;
Mouroux et al., 1997). Stimulation of the contralateral Pf nucleus induces the opposite effects said to be due to the activation of the thalamic reticular nucleus and the subsequent inhibition of the ipsilateral Pf nucleus and STN (Mouroux et al., 1995; Feger et al., 1997; Mouroux et al., 1997).

**Inhibitory potentials and hyperpolarization**

IPSPs generated by pallidal afferents from the GPe comprise the most important inhibitory mechanism controlling STN activity. Almost every cell in the STN responds to pallidal GABAergic stimulation (Overton et al., 1995). In fact, the pattern of STN response depends on the inhibitory activity provided by the afferents. Small IPSPs simply promote phase-dependent delays in firing between spikes, culminating with desynchronization (Bergman et al., 1985; Bergman et al., 1994; Wichmann et al., 1994a). Although electrophysiological somatotopy has been reported in the STN (arm, leg and orofacial representations, respectively, in the lateral, medial and dorsolateral regions of the nucleus), studies in which a large number of cells were assessed have described that neurons related to specific joints (i.e. shoulder, elbow, wrist, hip, knee, ankle) are not restricted to a single region of the STN but located in various sites within the nucleus (DeLong et al., 1985; Bergman et al., 1994; Wichmann et al., 1994a).

During normal movement, GABAergic activation is asynchronous and provides a small contribution to burst firing or oscillatory activity. In fact, asynchronous feedback inhibition from GPe to STN acts to limit excitatory drive (Bevan et al., 2000). Normally, local GPe neurons possess strong collateral activity, inhibiting synchronization and providing the basis for parallel activity. If striatal afferents provide an inhibition stronger than the collateral activity, however, a more regular and synchronized pattern ensues, enhancing the number of bursting episodes in the GPe and STN (Bevan et al., 2002b).

**Circuit oscillations**

Co-culture studies indicate that the STN-GPe circuit possesses intrinsic oscillatory properties (Plenz and Kital, 1999). Under these circumstances, however, the rhythm of the oscillations is low, usually around 0.4–1.2 Hz, due to the absence of the influence of afferent innervation (Plenz and Kital, 1999). In vivo, STN neurons fire in low-frequency bursts during slow wave sleep, when the cortical activity is synchronized in the delta range (Magill et al., 2000, 2001; Urbain et al., 2000; Wichmann et al., 2002). Cortical ablative procedures (but not the topical application of GABAergic agonists in the STN) interrupt these events, emphasizing the importance of cortico-subthalamic circuits in the genesis of these patterns (Urbain et al., 2000, 2002). In intact, untreated animals, only a few units oscillate above 4 Hz (~4%) (Bergman et al., 1994; Wichmann et al., 1994a). Low-frequency rhythms are relevant for the sleep-arousal cycle and for the reinforcement of synaptic connectivity (Amzica and Steriade, 1995; Charpier et al., 1999; Wichmann et al., 2002).

**Units related to body and eye movements**

It is estimated that between 30 and 50% of STN neurons are related to movement. Most of these units are localized in the dorsal half of the nucleus and are activated by passive and/or active movements of single contralateral joints (DeLong et al., 1985; Bergman et al., 1994; Wichmann et al., 1994a). Although electrophysiological somatotopy has been reported in the STN (arm, leg and orofacial representations, respectively, in the lateral, medial and dorsolateral regions of the nucleus), studies in which a large number of cells were assessed have described that neurons related to specific joints (i.e. shoulder, elbow, wrist, hip, knee, ankle) are not restricted to a single region of the STN but located in various sites within the nucleus (DeLong et al., 1985; Bergman et al., 1994; Wichmann et al., 1994a).

Nearly 20% of the neurons recorded in the STN are responsive to eye fixation, saccadic movements or visual stimuli (Matsumura et al., 1992). Most of these units are primarily found in the ventral part of the STN and participate in circuits that involve the frontal eye fields, the caudate nucleus, the GPe and the SNr. Activation of the STN drives SNr activity, which subsequently inhibits the superior colliculus, allowing the maintenance of eye position on an object of interest or the recovery of eye fixation once a saccade is executed (Matsumura et al., 1992).

**Stimulation and inhibition of STN activity**

**STN stimulation**

The application of GABAergic antagonists in the STN reduces the influence of pallidal inhibitory inputs. Under these circumstances, as well as with low frequency stimulation, an increase in metabolic and electrophysiological activity is generally observed not only in the STN, but also in SNr, GPi and GPe (Hammond et al., 1978; Robledo and Feger, 1990; Blandini et al., 1997).

Low frequency stimulation of the STN evokes a mixed response inducing EPSPs and IPSPs in the SNc, respectively, through direct STN-SNc and poly-synaptic pathways (Iribe et al., 1999). As a net effect, however, excitatory responses predominate, leading to an increase in the activity of SNc cells and the subsequent release of dopamine (Rosales et al., 1994). Indeed, bursting activity in the STN induces a bursting pattern in the SNc, increasing the release of dopamine from terminals, thereby influencing the activity of the basal ganglia and cortex (Smith and Grace, 1992; Chergui et al., 1994).

**STN inhibition**

Subthalamic lesions or the topical administration of GABAergic agonists regularize the firing patterns in the
globus pallidus and SNr, decreasing the overall electrophysiological and metabolic activity within these structures as well as in the PPN (Robledo and Feger, 1990; Ryan and Sanders, 1993; Blandini and Greenamyre, 1995; Guridi et al., 1996; Breit et al., 2001). In non-human primates, excitotoxic lesions of the subthalamic nucleus reduced the mean discharge rate of GPe (from an average of 69.8–47.4 Hz) and GPe (from an average of 63.6–41 Hz) neurons (Hamada and DeLong, 1992b).

Due to its relevance in neurosurgery, stimulation of the STN at high frequencies (HFS) has been investigated as an additional strategy to reduce STN activity. In a study that applied STN-HFS for 5 s, firing rates, after the stimulation was discontinued, were decreased in the STN, GPe, GPi and SNr, and increased in the ventrolateral nucleus of the thalamus (Benazzouz et al., 2000b). This study, however, did not address what occurs during STN stimulation.

STN-HFS induces alterations in the levels of neurotransmitters in basal ganglia structures. Glutamate increases in the GPi and SNr and dopamine increases in the striatum, whereas the levels of GABA increase in the SNr (Windels et al., 2000; Bruet et al., 2001).

**Behavioural effects of STN stimulation and lesions**

**STN stimulation**

In rodents, STN excitation through the topical infusion of GABAergic antagonists induces postural asymmetry and abnormal movements (i.e. jumping, axial torsion, and head and limb movements), but no significant locomotion activity (Dybdal and Gale, 2000; Perier et al., 2000). However, if high current is delivered to the nucleus or high concentrations of GABAergic antagonists are applied, abnormal movements such as dyskinesias can be elicited (Perier et al., 2002; Salin et al., 2002). In primates, dyskinesias and abnormal movements have recently been described with high frequency stimulation of the STN, whereas low frequency stimulation did not induce any behavioural effects (Beurrier et al., 1997).

**Ballism and lesion of the STN**

In the clinical scenario, ballisms are characterized by irregular, coarse, violent movements of the limbs (mainly proximal muscles) (Dewey and Jankovic, 1989). Although the classical description is related to cerebrovascular accidents in the subthalamic nucleus, diverse aetiologies in various regions of the brain can result in these abnormal movements (Dewey and Jankovic, 1989; Lee and Marsden, 1994; Ristic et al., 2002). The renaissance of functional neurosurgery for movement disorders and the suitability of the STN as a target have raised an important concern regarding subthalamotomies and the possible emergence of these involuntary movements.

In animals, ballism, as well as choreic and athetoid movements of the contralateral hemibody, are elicited after lesions or the topical application of GABAergic agonists in the STN (Hammond et al., 1979; Crossman et al., 1980; Beurrier et al., 1997). Although old studies have stated that >20% of the STN had to be compromised for the occurrence of abnormal movements (Whittier and Mettler, 1949), more recent studies have suggested that focal transitory dyskinesias can be evoked with lesions that involve only 4% of the nucleus (Crossman, 1987; Hamada and DeLong, 1992a; Guridi and Obeso, 2001).

Aside from the size of the lesions, their precise location seems to be important for the development of abnormal movements. Small lesions in STN efferents induce ballism, whereas lesions that spill over the STN to compromise the inner part of the pallidum and its respective fibre systems, i.e. in the Fields of Forel, do not induce involuntary movements (Whittier and Mettler, 1949; Crossman, 1987; Hamada and DeLong, 1992a; Barlas et al., 2001; Lozano, 2001; Doshi and Bhatt, 2002). This is likely to be related to the observation that pallidal or pallidal outflow pathway lesions are highly effective in suppressing dyskinesias (Lozano, 2001).

**STN and Parkinson’s disease**

STN activity in parkinsonian animals and patients with Parkinson’s disease is characterized by an augmented synchrony, a tendency towards loss of specificity in receptive fields, and a mildly increased firing rate with bursting activity (Hutchison et al., 1998; Magarinos-Ascone et al., 2000; Magnin et al., 2000; Levy et al., 2002b). In non-human primates treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), the firing rate of subthalamic neurons increases to an average of 26 Hz (Bergman et al., 1994). In addition, the number of STN neurons that demonstrate oscillatory activity increases from only a few units to ~20% (Bergman et al., 1994).

In Parkinson’s disease patients, the average frequency of discharge of STN neurons in most studies ranges from 35 to 50 Hz (Hutchison et al., 1998; Bejjani et al., 2000; Magarinos-Ascone et al., 2000; Magnin et al., 2000; Levy et al., 2002b; Pralong et al., 2002; Sterio et al., 2002). Most neurons in the STN in Parkinson’s disease patients fire irregularly, although regularly firing neurons and oscillatory cells are not uncommon. Oscillatory neurons usually present a rhythmic activity and may or may not be time-locked with tremor. Recorded units that are synchronous to the clinical tremor exhibited by the patients are called tremor cells (frequency of oscillation around 4–8 Hz in patients with Parkinson’s disease). Movements elicited by the patients as well as high frequency stimulation of the STN, decrease not only the patients’ tremor but also the related tremor cell activity.

Another important characteristic of STN neurons in Parkinson’s disease is their relationship to motor activity. Fifty-five per cent of STN cells in Parkinson’s disease
patients react to active or passive movements, mostly of single contralateral joints. In addition, however, 24% of the units also respond to ipsilateral or multiple joint movements, reflecting the increase in receptive field size and loss in specificity previously mentioned (Abosch et al., 2002). Most movement-related cells (65%) are located in the anterodorsal portion of the STN, which appears to be the most effective target for high frequency stimulation in terms of clinical benefits (Abosch et al., 2002; Lanotte et al., 2002; Saint-Cyr et al., 2002; Starr et al., 2002).

Oscillatory patterns

After dopamine depletion, the STN-GP circuit becomes more reactive to the influence of the activity of cortical inputs (Magill et al., 2000, 2001). Even after cortical deafferentation however, almost 20% of STN units continue to display oscillatory patterns, suggesting that dopamine depletion provokes a surge of independent rhythms in the STN-GPe network (Magill et al., 2001).

Three main patterns of circuit oscillations have been reported in Parkinson’s disease: below 10 Hz (4–8 Hz), between 15 and 30 Hz and between 70 and 85 Hz (Brown et al., 2001; Cassidy et al., 2002; Levy et al., 2002a). As previously mentioned, STN cells with oscillatory frequencies below 10 Hz (4–8 Hz) are highly related to the characteristic parkinsonian tremor, which also oscillates between 4 and 8 Hz. In Parkinson’s disease patients, oscillations between 15 and 30 Hz (which are also found in the STN) synchronize motor circuits and are related to the mechanisms of the bradykinesia and akinesia (Brown et al., 2001; Levy et al., 2002a). Voluntary movements and the administration of dopaminergic agonists attenuate this pattern of oscillations. Oscillations in the 70–85 Hz range, in contrast, occur during movement and after treatment with dopaminergic agonists, and are apparently important for an accurate execution of motor programs (Magill et al., 2001; Cassidy et al., 2002; Levy et al., 2002a).

STN hyperactivity

In the current model of Parkinson’s disease, the preponderance of STN hyperactivity has been attributed to the underactivation of the GPi due to abnormalities in the indirect pathway. Recent studies, however, have provided evidence that does not fully support this hypothesis, suggesting that other brain regions, such as the cerebral cortex and the Pf nucleus of the thalamus, may also be responsible for the increased STN activity observed after dopamine depletion (Hassani et al., 1996; Feger et al., 1997; Levy et al., 1997; Orieux et al., 2000; Orieux et al., 2002). Independent of the mechanism, the pathological STN drive in parkinsonian states, which includes variations in firing pattern, enhanced oscillatory and synchronized activity, modifies the overall electrophysiological and metabolic activity in the SNr, GPi, GPe and PPN, disrupting the normal physiology of the basal ganglia (Hammond et al., 1978; Robledo and Feger, 1990; Blandini et al., 1997; Breit et al., 2001). In the SNc, STN overdrive is predicted to enhance bursting activity and increases the release of dopamine. Although this has been considered an initial compensatory mechanism after dopamine depletion, the excessive release of glutamate that follows STN hyperactivity may also lead to excitotoxic damage, which is potentially devastating, since it could promote a further loss of dopaminergic neurons, accelerating the progression of the disease (Piallat et al., 1996; Bezard et al., 1999; Piallat et al., 1999).

A number of therapeutic strategies have been proposed to re-establish the normal patterns of activity within the BG and suppress STN pathological activity. These include the administration of dopaminergic agonists and glutamate blockers, focal delivery of neurotrophic factors, change in the phenotype of STN neurons, lesions and high frequency stimulation of the STN (Bergman et al., 1990; Aziz et al., 1991; Klockgether et al., 1991; Wichmann et al., 1994b; Limousin et al., 1995; Hutchison et al., 1998; Vila et al., 1999; Benabid et al., 2000a,b; Blandini et al., 2001; Levy et al., 2001; Luo et al., 2002; Gill et al., 2003; Nutt et al., 2003).

Dopamine and the parkinsonian STN

The specific role of dopamine in the STN in parkinsonian states is complex and depends on different receptor subtypes and various anatomical pathways. In rodents, the topical application of apomorphine and D2 agonists increases STN activity, whereas D1 agonists exert the opposite effect (Hassani and Feger, 1999). Conversely, the systemic administration of apomorphine and D2 agonists reduces, whereas D1 agonists increase the firing rate of STN neurons (Kreiss et al., 1997; Ni et al., 2001). In Parkinson’s disease patients the administration of apomorphine does not change the mean frequency of discharge in non-oscillatory cells, but significantly reduces the number of units displaying oscillatory behaviour (Levy et al., 2001).

In animal models of parkinsonism and patients with Parkinson’s disease, the administration of dopaminergic agonists partially reverses some of the abnormalities observed in the subthalamic nucleus, improving the major motor symptomatology related to these conditions (Vila et al., 1996; Kreiss et al., 1997; Hutchison et al., 1998; Hassani and Feger, 1999; Levy et al., 2001).

Lesions and high frequency stimulation

Both STN lesions and high frequency stimulation ameliorate the major motor symptoms of parkinsonism in humans and animal models of Parkinson’s disease and reverse certain electrophysiological and metabolic consequences of dopamine depletion (Bergman et al., 1990; Aziz et al., 1992; Benazzouz et al., 1993; Benazzouz et al., 1996; Vila et al., 1996; Kreiss et al., 1997; Hutchison et al., 1998; Hassani and
Subthalamic nucleus

Feger, 1999; Benazzouz et al., 2000a, b; Barlas et al., 2001; Levy et al., 2001; Lopiano et al., 2001). Based on these findings, it has been suggested that high frequency stimulation inhibits STN output. Recent studies, however, have challenged this view. In non-human MPTP primates, high frequency stimulation of the STN at therapeutic levels drove GPi (from an average of 63.2 to 81.7 Hz) and GPe (from an average of 50.4 to 65.4 Hz) activity (Hashimoto et al., 2003). These data suggest to the contrary that STN stimulation drives STN output.

In patients with Parkinson’s disease tremor and rigidity improve to a larger extent, whereas akinesia, gait disturbances and postural abnormalities are less responsive. Involuntary movements induced by L-dopa respond dramatically to surgery. The mechanism through which high frequency stimulation of the STN ameliorates these symptoms is still unclear and controversial (reviewed in Dostrovsky and Lozano, 2002; Lozano et al., 2002).

The main disadvantage reported for lesions to the STN, is the potential risk for the development of choreiform abnormal movements. As for normal primates, however, it appears that only STN lesions confined within borders of the nucleus induce abnormal movements, whereas lesions that extend to the pallidal-related fibre systems do not (Crossman, 1987; Hamada and DeLong, 1992a; Barlas et al., 2001; Lozano, 2001; Doshi and Bhatt, 2002; Vilela Filho and Silva, 2002). Supporting this statement, in surgical procedures, dyskinesias are sometimes observed during the insertion of stimulation probes, which may induce a small lesion effect in the STN. Moreover, dyskinesias and choreiform movements can be elicited with high frequency stimulation in the subthalamic nucleus during the adjustment of the electrical settings in patients treated with STN deep brain stimulation (Benabid et al., 2000a).

STN and degenerative disorders
Pathological abnormalities in the subthalamic nucleus have been described in several neurodegenerative disorders. Nevertheless, most studies consist of small case series and case reports and the exact role of the STN in these conditions is still disputed. Patients with progressive supranuclear palsy (PSP) present an important volumetric reduction of the STN as well as significant neuronal loss (45–85%), gliosis, neurofibrillar tangles, and the accumulation of Tau protein in astrocytes (Hardman et al., 1997; Togo and Dickson, 2002). Patients with corticobasal degeneration present similar findings, although to a lesser extent (Dickson, 1999). Patients with pallidodentroluysian atrophy also present neuronal loss and gliosis in the STN (Mori et al., 2001). STN neurofibrillary tangles have been reported in argyrophilic grain disease and advanced Alzheimer’s disease (Mattila et al., 2002). In Parkinson’s disease, the volume and the number of neurons in the STN is said to be unaffected (Hardman et al., 1997).

Summary
The STN is a major glutamatergic structure within the basal ganglia, strongly influencing the activity of its major output channels. It has been involved in the physiopathology of parkinsonian states and the disruption of its pathological activity, either through lesions, the topical administration of GABAergic agonists, or high frequency stimulation, partially reverses some of the clinical, electrophysiological and metabolic abnormalities related to Parkinson’s disease.

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