

## REVIEW

# SIX QUESTIONS ON THE SUBTHALAMIC NUCLEUS: LESSONS FROM ANIMAL MODELS AND FROM STIMULATED PATIENTS

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**Abstract**—Since the early 90s, the subthalamic nucleus (STN) has started to be the subject of an increasing interest not only in the community of the basal ganglia scientists but also for neurosurgeons and neurologists, thanks to the development of the surgical treatment for Parkinson's disease. The involvement of the STN in cognitive and motivational processes has been demonstrated since, and psychiatrists are now considering this small structure as a possible target for the treatment of various disorders. In this review, we will address six questions to highlight (1) How increased knowledge has led us from a strictly motor model to an integrative one. (2) How knowledge acquired in animal models can be similar or (3) different from the effects observed in human patients. (4) How clinical trials are sometimes ahead of fundamental research carried out in animals, showing effects that could not be predicted on the basis of animal studies, thus questioning the relevance of some animal models, especially for psychiatric disorders. We will also address the possible future orientations (5) and how the use, or precaution not to use, certain key words in animal research dedicated to STN functions can lead to the omission of a certain amount of available data in the literature (6).

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**Key words:** basal ganglia, OCD, perseveration, motivation, DBS, high-frequency stimulation.

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**Abbreviations:** DBS, deep brain stimulation; HFS, high-frequency stimulation; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; STN, subthalamic nucleus; 5-CSRTT, 5-choice serial RT task.

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The subthalamic nucleus (STN) is a small structure of the basal ganglia that has long been considered to be a relay in the treatment of motor-related information. Because of its dysregulation in Parkinson's disease, it has gained interest for the treatment of this disease in the 90s. Its anatomic connectivity has been scrutinized into more details to reveal an interesting position at the nexus of motor, associative, and limbic pathways. This potentially integrative function of STN has also contributed to consider it as a possible target for the treatment of various other neurological and psychiatric disorders. When asked to discuss functions and dysfunctions of STN for the present review, we found interesting to avoid the classic review format of a list of experiments, showcasing the many functions in which the STN is involved. Instead, we chose to mix the inputs of a neuroanatomist, a neurobiologist using animal models, and a psychiatrist. We have attempted to summa-

rise in six questions how knowledge regarding the STN has evolved during the last 20 years, how fundamental research has contributed to some clinical improvement, and how, in turn, surgical developments can be helpful for fundamental research; many questions remaining unanswered.

### IS THE STN STILL THE CORPUS LUYSII?

The corpus Luysii has been discovered in 1865 as the “bandelette accessoire des olives supérieures (accessory band of the superior olives)” or occasionally as the “substance grise accessoire des olives supérieures” by the French neurologist Jules Bernard Luys (Luys, 1865). Although these naming contained some ambiguity, since the term “bandelette” referred to white matter but not a gray nucleus and the superior olives corresponded to the red nucleus, the description of Luys was unambiguously that of what is called nowadays the subthalamic nucleus or STN (Parent, 2002).

The first extensive systematic studies of the STN have been those of the group of Mettler, Whittier, and Carpenter (Mettler, 1945; Whittier, 1947; Whittier and Mettler, 1949a,b). At this stage obviously the role of the STN of Luys was definitely focused on motor control (Carpenter et al., 1950, 1968, 1981a,b; Carpenter and Carpenter, 1951; Carpenter and Mettler, 1951; Harman and Carpenter, 1951; Carpenter and Jayaraman, 1990).

Neuronal morphology in the STN was also studied in this period, with a debate to determine whether there were one or two neuronal types in the STN. Considering the 3D geometry of the dendritic arborizations, a distinction between radiated and elongated neurons (Rafols and Fox, 1976) was refuted (Yelnik, 1976; Yelnik and Percheron, 1979). Further studies of neuronal morphology in rodents (Hammond and Yelnik, 1983; Kita et al., 1983; Afsharpour, 1985) could not demonstrate either the presence of different neuronal types. There is therefore no plausible demonstration to date that the STN has different neuronal types.

The last twenty years of the 20th century (1983–1995) have been marked by an explosive creativity, which has given rise to decisive conceptual progresses in the neurological, neurosurgical, and neurobiological domains. In particular, it is in this period that the concept of a “basal ganglia system” specifically devoted to processing of cortical information and controlling of motor behavior began to stand out in the neuro-scientific community (see (Percheron et al., 1994) for review).

In 1976–1983, a chemical compound was fortuitously discovered by an American student in chemistry who tried to generate a synthetic drug product and by Langston who demonstrated that this 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was responsible of the death of dopaminergic neurons of the substantia nigra pars compacta (Langston et al., 1983; Langston and Ballard, 1983). This made it possible to develop an experimental model of Parkinson’s disease and to begin to understand the critical

role that the basal ganglia and notably the STN play in the pathophysiology of this disease.

Following this discovery, a model of the basal ganglia circuitry was proposed that explained both the hypokinetic effect of the death of dopaminergic neurons and the opposite hyperkinetic effect observed in Huntington’s disease (Albin et al., 1989; DeLong, 1990).

The first suggestion that the basal ganglia could process non-motor information was proposed in the parallel segregated model of Alexander and colleagues in which information arising from motor cortex, dorsolateral prefrontal cortex, and anterior cingulate cortex were transmitted by different parallel circuits along the basal ganglia (Alexander et al., 1986). The formal subdivision into motor, associative, and limbic territories that would process motor, cognitive, and emotional information was proposed in the model of Parent in 1990 (Parent, 1990), and then developed in his well-known review papers, one of which specifically devoted to the STN (Parent and Hazrati, 1995a,b). The existence of a ventral pathway that processes non-motor information was also put forward in rodents (Haber et al., 1985; Groenewegen and Berendse, 1990; Groenewegen et al., 1997). However, it is important to note that on the schematic representations of the parallel loops, the STN only appears on the motor circuit.

In the meantime, a series of researches on the implication of the STN in attentional and motivational processes in intact and 6-hydroxydopamine-lesioned rat were conducted (Baunez et al., 1995, 2002; Baunez and Robbins, 1997, 1999a,b) that demonstrated that the STN is not restricted to motor control but plays a crucial role in the processing of high-level cognitive functions.

While our knowledge developed in rodent and primate species, it was shown in human that high-frequency stimulation (HFS) of a deep brain structure could give similar clinical results as a definitive lesion of this structure (Benabid et al., 1987). Following experiments in the monkey (Bergman et al., 1990; Aziz et al., 1991; Benazzouz et al., 1993), HFS of the STN was applied successfully to human parkinsonian patients (Limousin et al., 1995). This discovery happened to initiate, at the end of the 20th century, another series of crucial discoveries demonstrating the role of the STN in non-motor functions in humans.

The subdivision of the basal ganglia into three functional territories arising from the cerebral cortex (Parent, 1990) has been confirmed in rodents (Groenewegen et al., 1993) and by using calbindin immunoreactivity in the monkey (François et al., 1994) and human (Karachi et al., 2002). As the STN does not express calbindin, the three functional territories have been demonstrated using axonal tracings from the GPe in the monkey (Karachi et al., 2005) and transferred by homology to the human STN (Yelnik et al., 2007). Although these territories in human remain to be demonstrated using specific methods applicable to living human subjects like Diffusion Tensor Imaging, several results recently obtained in the context of deep brain stimulation clearly demonstrated in human the role that the STN plays in non-motor functions: emotional processes (Kühn et al., 2005), hypomania (Mallet et al., 2007), ob-

sessive-compulsive disorders (Mallet et al., 2008), laughter (Krack et al., 2001), gambling (Ardouin et al., 2006).

Based on this new knowledge, models of the basal ganglia functioning, and specifically of the STN, have evolved so as to take into account its role in non-motor functions as action selection (Mink, 1996; Redgrave et al., 1999; Gurney et al., 2001a,b; Nambu et al., 2002; Nambu, 2004) or impulsivity (Frank et al., 2007).

At the present time the connections of the STN comprise both motor and non-motor components (Parent and Hazrati, 1995b; Hamani et al., 2004). Afferent pathways arise mainly from the lateral pallidum with three functional subdivisions, motor, associative, and limbic, from the cerebral cortex (mainly primary motor, supplementary motor, premotor), the parafascicular thalamic nucleus, the substantia nigra pars compacta, the pedunculopontine nucleus, and the dorsal raphe nucleus. The cortico-subthalamic projection is referred to as the “hyperdirect pathway” to which a specific functional role has been attributed in the basal ganglia circuitry (Nambu et al., 2002). Efferent projections of the STN are directed toward both segments of the globus pallidus, substantia nigra, striatum, and pedunculopontine nucleus.

#### And now? . . .

At the present time it is clear that the concept that the basal ganglia community has of the STN has dramatically evolved since its discovery by Jules Bernard Luys. Starting from a purely motor role, albeit not clearly understood, which would consist of avoiding an explosive over liberation of the motor activity, the so-called hemiballism, the “motor corpus Luysii” has now reached the status of a “subthalamic nucleus” being the central node of the basal ganglia (may be of the entire central nervous system?), a nexus (Mallet et al., 2007) that would play a crucial role in the cognitive and emotional control of behavior.

An intriguing challenge, however, is to understand how such a small nucleus with so small a quantity of neurons with regard to its cortical afferents (Bar-Gad et al., 2003; Yelnik, 2008) could be able to control so important behavioral functions.

The following parts of this review will deal with this totally new, open, and fascinating field of research, which proceeds in both its basic and clinical aspects and uses all experimental approaches available in rodents, primates, and human species.

### WHAT HAVE ANIMAL DATA PREDICTED THAT HAS BEEN SEEN IN HUMAN SUBJECTS?

#### Motor functions

As developed previously, the STN has long been considered to be a motor structure of which the lesion induced hemiballism or ballism. In that case, detailed previously, clinical observation had anticipated animal experiments to show that STN lesion could induce ballism (Whittier, 1947) that could be replicated in the monkey (Whittier and Mettler, 1949a,b). It is also the known involvement of STN in motor control that was responsible for the current success-

ful treatment of Parkinson's disease (PD). Indeed, experimental data have led to the conclusion that in cases of DA depletion such as PD, the STN was hyperactive (DeLong, 1990). The pioneer following experiment was thus to lesion the STN in an animal model of PD. This was first tested in the MPTP monkey with success on gross motor behavior (Bergman et al., 1990), followed by pharmacological inactivation of STN outputs (Graham et al., 1990) and then by STN HFS with a beneficial effect on muscular rigidity, bradykinesia, and general motor abilities in MPTP monkeys (Benazzouz et al., 1993). This set of data obtained in monkeys was further confirmed in a rat model of parkinsonism, showing that STN lesion could reduce akinesia assessed by the measure of reaction time (Baunez et al., 1995). The primate studies lead to the application of STN HFS in parkinsonian patients, which was first initiated by Prof. Benabid in Grenoble and proved to be successful for the treatment of motor deficits (Limousin et al., 1995). Pharmacological inactivation of the STN by either lidocaine or muscimol was later proven to have beneficial effect on motor deficits of PD patients, thus supporting the idea that STN HFS mimics partly an inactivation (Levy et al., 2001).

While in the intact marmoset unilateral lesion of the STN was shown to induce postural asymmetry (Andr n et al., 1995), in hemiparkinsonian rats it induced body axis curling (Henderson et al., 1999), thus suggesting that the STN might not be the best target to treat axial and postural deficits. This is in line with the clinical observations (Su et al., 2002; Guehl et al., 2006) that have led neurosurgeons to target other structures in addition to the STN for the treatment of these gait and axial disorders (Lozano and Snyder, 2008).

#### Non-motor functions

*Attention.* The role of STN in arousal, wakefulness, and alertness has been suggested in the late 60s based on studies carried out in the cat (Naquet et al., 1966; Lindsley et al., 1970). This line of research has been abandoned until the regain of interest in the STN as a therapeutic target for the treatment of PD that occurred during the 90s, as described previously in the text.

The involvement of STN in attention was first tested in rats performing the “5-choice serial RT task” (5-CSRTT) (Baunez and Robbins, 1997). Rats were trained to wait and detect a brief visual stimulus that was randomly presented in five possible different locations. The animals had to divide their attention between these five possible choices and then go and poke in the appropriate location to obtain a food reward. The movement to make for the rat is equivalent whatever the hole chosen. Therefore, the measure of accuracy in the appropriate hole is considered as an index of attentional performance and not related to movement (Robbins, 2002). In this specific visual attentional task, we have shown that bilateral excitotoxic lesions of the STN seriously impaired accuracy, thus suggesting an attentional deficit (Baunez and Robbins, 1997). When increasing the stimulus duration to decrease the attentional load, performance was slightly improved, showing that this deficit was related to attention (Baunez and Rob-

bins, 1997). Decreased accuracy in the same task was also observed after pharmacological inactivation of the STN (Baunez and Robbins, 1999b). Furthermore, a disconnection between the medial prefrontal cortex and the STN, through a lesion of the prefrontal cortex on one side and the STN on the contralateral side, provided the first evidence of a functional role for the hyperdirect pathway in the attentional deficits observed in this behavioral task. Indeed, the disconnection induced similar deficits on accuracy to those observed after bilateral STN lesions (Chudasama et al., 2003).

From these rat data, the STN appears to be involved in attentional processes, possibly via the hyperdirect pathway. Some clinical studies assessing the cognitive functions of PD patients who underwent STN deep brain stimulation (DBS) have also reported attentional decline (Saint-Cyr et al., 2000; Mallet et al., 2007; York et al., 2008). Interestingly enough, bilateral STN HFS in the intact or parkinsonian rat only induced a transient deficit (Baunez et al., 2007).

*Inhibitory control–impulsivity–compulsivity.* As previously mentioned, increased premature responding was observed after STN lesions in a simple RT task, a deficit that may reflect a lack of inhibition control (Baunez et al., 1995). This result has been replicated after a unilateral STN lesion (Phillips and Brown, 1999).

It was also shown that bilateral lesions and pharmacological inactivation of STN increase premature responses in the 5-CSRTT described previously (Baunez and Robbins, 1997, 1999b). In line with these deficits observed in the rat, STN HFS applied in PD patients was shown to impair response inhibition in a go/no go task (Ballanger et al., 2009) or in the Simon reaction time task (Wylie et al., 2010), in line with the rat lesion studies and in line with the computational model suggesting that the STN could play a critical role in “withholding a response” (Frank et al., 2007). A more recent study confirmed this effect of STN HFS on go/no go performances but provided further details, showing that the limbic territory of STN (i.e. ventral) played a greater part in the control of inhibition than the motor territory (i.e. dorsal) (Hershey et al., 2010). This deficit in lack of inhibitory control after STN inactivation can be also related to the suicide rate that has been shown to increase in patients subjected to STN HFS and could be explained by the fact that the patients with STN DBS have less inhibition that would prevent them to commit suicide (Voon et al., 2008).

Although there is no satisfying animal model of OCD available to date, a few studies have shown that STN HFS could have a beneficial effect on some measures of compulsivity or repeated-stereotyped behavior in rodents (Winter et al., 2008a,b; Klavir et al., 2009) and in a non-human primate (Baup et al., 2008). Therefore, it has been hypothesized that stimulation of the limbic/anterior part of the STN that has direct connections to the limbic GPe and indirect ones to the striatum (François et al., 2004; Karachi et al., 2005) could have an effect on several OCD symptoms, especially compulsions, as it has been effectively

shown in humans (Mallet et al., 2002, 2008; Fontaine et al., 2004). Nevertheless, the relevance of these stereotypes otherwise called compulsive-like behaviors may be questioned as a measure of compulsion.

*Motivation.* The anatomical data confirming that STN is part of the limbic loop involving the prefrontal cortex, the nucleus accumbens, and the ventral pallidum suggest that STN should be involved in the processing of motivational information. First evidence was provided by electrophysiological recording of STN neurons in the monkey performing an oculomotor task and reporting changes of activity when the animal was expecting its reward (Matsumura et al., 1992). This was further confirmed in the monkey (Darbakay et al., 2005) and further supported by behavioral data obtained in the rat showing that STN lesions increased dramatically the number a perseverative responses in the food magazine where the animals collect their reward in the 5-CSRTT (Baunez and Robbins, 1997). Further studies assessing various forms of motivation in the rat confirmed that STN lesions do not increase hunger, but increase incentive motivation for food (Baunez et al., 2002, 2005; Uslaner and Robinson, 2006; Uslaner et al., 2008). This effect could then result in the clinical observations reporting hyperphagia or hypersexuality after STN injury (Absher et al., 2000; Barutca et al., 2003) or weight gain in PD patients subjected to STN HFS (Barichella et al., 2003; Macia et al., 2004; Montaurier et al., 2007; Bannier et al., 2009; Sauleau et al., 2009; Walker et al., 2009; Moghadasi and Boshtam, 2010). Although numerous publications report weight gain, the motivational state of these patients has been rarely studied to favor instead metabolic or motor explanation. Interestingly, a recent report studying binge-eating in PD patients has highlighted the fact that the over-eaters were indeed those patients subjected to STN DBS (Zahodne et al., 2011).

Finally, it has been shown that STN lesions or HFS not only increase motivation for food, but they reduce motivation for drugs of abuse such as cocaine (Baunez et al., 2005; Rouaud et al., 2010). In line with this observation, although there are no data available regarding traditional drugs of abuse in PD patients subjected to STN HFS, there are clinical reports of patients addicted to their dopaminergic treatments (also called Dopamine Dysregulation Syndrome; DDS) showing improvement of their addiction under STN HFS (Witjas et al., 2005; Ardouin et al., 2006).

*Working memory.* Impairment of different forms of working memory has been reported after STN lesion in the rat (Baunez et al., 2001; El Massioui et al., 2007), that has also been found in PD patients under STN HFS (Hershey et al., 2003, 2010).

Although the animal models using chronic lesions, acute injections or acute DBS might be considered as not equivalent to the chronic DBS applied in patients, we have reviewed here an impressive list of facts supporting the involvement of STN in motor, associative, and limbic functions, whatever the model or the way to manipulate the STN.

## WHAT HAVE ANIMAL DATA PREDICTED THAT HAS NOT BEEN SEEN IN HUMAN SUBJECTS?

### Motor functions

It has been shown that inactivation of STN neurons by local muscimol injection induces orofacial dyskinesia in the rat (Mehta et al., 2005), but such behavioral effect has not been reported in patients subjected to STN manipulation.

### Non-motor functions

**Attention.** We have described the attentional deficits observed in rats after STN inactivation previously (Baunez and Robbins, 1997, 1999b; Baunez et al., 2007). However, some studies of PD patients show no attentional detrimental effect of STN HFS (Ardouin et al., 1999; Brusa et al., 2001) or even improvements (Fimm et al., 2009). It may well be due to the fact that HFS does not necessarily mimic an inactivation of the structure, as shown by fMRI studies (Hershey et al., 2003) or reviewed by Gubellini et al. (Gubellini et al., 2009).

**Compulsions.** Compulsive behavior, a form of a dysfunctional control of inhibition, is often linked with addiction when the drug consumption switches from recreational use to compulsive use. In animals, it is classic to qualify as “compulsive-like behavior” repetitive responses that are not necessarily appropriate. When testing the effects of bilateral STN lesions in rats performing the 5-CSRTT, we have observed an increased level of perseverative responses toward both the response locations and the magazine where the animals collect the food reward. These results suggest that lesioning the STN can lead to a form of “compulsive-like” behavior (Baunez and Robbins, 1997). Interestingly, this perseverative-compulsive-like behavior was also observed after bilateral STN HFS (Baunez et al., 2007) and after pharmacological inactivation of the STN (Baunez and Robbins, 1999b). These observations seem antagonistic to the fact that STN HFS could have a beneficial effect to treat OCD (Mallet et al., 2002, 2008).

**Inhibition.** Another form of inhibitory control can be assessed using the stop task, a task during which the subject is requested in some trials to stop an action that is already initiated. In this task, it was shown in human subjects that STN activation was correlated with faster stopping abilities (Aron and Poldrack, 2006). In line with this observation, using an equivalent task in the rat, we have shown that STN lesions prevent the animals to be able to stop an ongoing action (Eagle et al., 2008). However, while STN inactivation prevents rats to stop, STN HFS applied in PD patients improves their stopping abilities (van den Wildenberg et al., 2006).

**Memory.** As for attentional processes, although the animal data are consistent and find a slight deficit in working memory after STN lesions (Baunez et al., 2001; El Massioui et al., 2007), cases of improvement have been reported in the clinical literature (Pillon et al., 2000; Rivaud-Pechoux et al., 2000). Whether or not this improvement is due to a direct effect of STN DBS or might be related to the

DA imbalances in the brains of these patients remains to be elucidated.

**Motivation–Addiction.** We have shown that STN lesions could decrease motivation for alcohol in “low drinker” rats, but increase it in “high drinker” rats (Lardeux and Baunez, 2008). This result suggests that inactivation of the STN applied in patients with a history of alcoholism could be at risk. However, it is interesting to note that no report of alcoholism after STN HFS has been reported to date.

**Sexual behavior.** We have described previously how STN lesions can increase motivation for food and decrease motivation for drugs of abuse. Considering sexual behavior, we might have expected to see a higher sexuality following STN lesion in rats if the dissociation were to rely on “natural reward” versus “drugs of abuse.” However, a study has shown that sexual behavior was stopped after a lesion in the STN area (Maillard and Edwards, 1988). This result contrasts with the hypersexuality reported in PD patients with STN DBS (Romito et al., 2002; Doshi and Bhargava, 2008) and the case of hypersexuality reported after STN infarct (Absher et al., 2000).

## WHAT HAVE ANIMAL DATA NOT PREDICTED THAT HAVE OCCURRED?

### Motor functions

Although we have mentioned previously orofacial dyskinesia in the rat after STN inactivation, it is obviously impossible to assess speech ability in animal models. It is interesting to note here that in PD patients, STN HFS can improve some motor components of speech production, but can also worsen speech intelligibility (Pinto et al., 2004). One problem that has been observed in patients that was not reported in animal models relates to gait. PD patients have indeed gait problems that are not sufficiently improved by STN HFS (Bloem et al., 2004). This has led to the search of other targets to alleviate this problem, and the current target proposed is the pedunculopontine nucleus (Pahapill and Lozano, 2000; Plaha and Gill, 2005; Stefani et al., 2007; Piallat et al., 2009; Ferraye et al., 2010; Hamani et al., 2011).

It has been extensively documented that STN HFS has a beneficial effect on motor performance in PD patients. However, the first study applying STN HFS in hemiparkinsonian rats performing a choice reaction time task has shown that STN HFS could reduce motor initiation deficits in the animals still able to perform the task after DA depletion, but was unable to have an “awakening” effect in those animals not able to perform the task after DA depletion (Darbaky et al., 2003). Although this discrepant result may have questioned the validity of the STN HFS technique in the rat, the beneficial effect of STN HFS was however demonstrated on more basic motor measures in the same study (Darbaky et al., 2003), and further studies reported in this review have proven to induce effects of STN HFS in the rat in line with what was observed in human subjects. The critical question raised by the pioneer rat study by Darbaky et al. was the efficacy of STN HFS when a cog-

nitive load was important for motor performance, highlighting the role of STN in non-motor functions.

### Non-motor functions

STN HFS has been shown to induce cognitive and behavioral modifications in humans such as hypomania (Ulla et al., 2006; Voon et al., 2006; Mallet et al., 2007) and improvement of obsessive-compulsive symptoms in both PD and obsessive-compulsive disorder patients (Mallet et al., 2002, 2008). In PD patients, STN HFS is also known to induce cognitive deficits in executive function (Witt et al., 2004), and working memory (Hershey et al., 2004), as well as emotional deficits in the recognition of facial emotion (Dujardin et al., 2004; Biseul et al., 2005) and subjective emotional experience (Vicente et al., 2009). As mentioned previously, although some cognitive deficits were anticipated based on the animal literature, the latter observations suggest that the STN is involved in the processing of non-motor information related to emotional aspects of behavior. Some emotional aspects are difficult to record in animal experiments, although skin conductance, cardiac frequency, anxiety, stress, and fear conditioning are used to assess emotions. None of these have yet been reported after STN manipulation in animal models. Motivational aspects are particularly interesting as they can be recorded in animal experiments as well as in human patients, and this constitutes a highly promising aspect of incoming researches. The processes through which human subjects integrate emotional and motivational information with motor and cognitive information is not yet fully understood, but it seems likely that the STN occupies an important position in this process (Mallet et al., 2007).

**Cognition.** In the assessment of cognitive functions in PD patients with STN HFS, the most robust finding is the decline in word fluency, although declines of various other executive functions have been also reported (Voon et al., 2006). Moreover, specific patient subgroups (e.g. older patients, patients with moderate cognitive impairment before surgery) may be at greater risk of sustaining cognitive and neurobehavioral deficits, that raises the question of an interaction between the disease and the HFS STN, making these observations less relevant regarding the physiologic function of the STN.

**Mood and motivation.** Given the difficulty to assess it in animal models, apathy could not be predicted to occur after STN HFS. Many cases of postsurgical apathy have been reported (Krack et al., 1998; Dujardin et al., 2004; Funkiewiez et al., 2004). Apathy is usually improved by starting or increasing dopaminergic treatment even if the patient's motor state does not require it (Funkiewiez et al., 2004). In some cases it persists in spite this type of treatment and may be associated with a frontal lobe-like cognitive decline, suggesting that this symptom results from the neurodegenerative process. Finally, OCD patients with STN HFS did not show apathy (Mallet et al., 2008), this therefore suggests that apathy is a multifactorial process that could be the result of an interaction between dopaminergic denervation and STN stimulation.

Stimulation of anteromedial STN induces a hypomanic state without any difference regarding the effect on motor activity as compared with more posterior and dorsal stimulation (Mallet et al., 2007). Functional imaging data indicate increased regional blood flow concomitant with the hypomanic state in the antero-ventral thalamic nucleus (implied in limbic circuitry) and a decrease in the right prefrontal anteromedial cingulate gyrus—thereby replicating the map of cerebral activity modifications seen during mood swings. This hypomanic state induced by the STN HFS represents a human complex behavior including some symptoms that could have been predicted by animal studies (e.g. impulsivity). However, it was also characterized by euphoria and pressure of speech, which could not have been anticipated. On the basis of our knowledge of STN organization, this observation demonstrates the way in which this nucleus, despite its small size, can receive and process a variety of different information.

**Emotional processing.** The existence of emotional processing within the STN at the level of neuronal assemblies activity has been shown in PD patients (Kühn et al., 2005; Brücke et al., 2007). Local field potentials were recorded in the STN of Parkinsonian patients implanted for deep brain stimulation, while they were looking at emotionally salient pictures. By using low-arousing and high-arousing pleasant pictures, it has been shown that the STN is implicated in valence-related emotional processing, suggesting the existence of emotional processing within the basal ganglia that notably may be altered by HFS leading to emotion recognition deficits (Dujardin et al., 2004) and/or behavioral complications. To date, no data from animal studies are available regarding the role of STN in emotional processes.

**Social cognition.** STN HFS in PD patients has been reported to hinder the ability to infer the mental states of others, notably modulating a distributed network known to subtend Theory of Mind (Péron et al., 2010). Another study showed that the STN is implicated in action observation and action understanding, raising the hypothesis that the STN and, more generally, basal ganglia could be part of the mirror system (Marceglia et al., 2009). In this study, STN local field potentials have been recorded in parkinsonian patients implanted for deep brain stimulation. A film representing a hand grasping an object was presented to the patients, followed by pictures representing either action-related or independent objects. Similar modulation of STN-beta oscillations have been described for action observation and for static action-related objects. On the contrary, pictures of objects that were not related to the action induced different modifications of activity in the same frequency band. Moreover, oscillatory activity was differentially modulated in the different conditions, with dissociation between the low-beta and high-beta band. The hypothesis of an implication of the STN in the mirror system is original and enhances the model of mental functions related to STN functioning. This might contribute to explain some of the behavioral disturbances related to STN stimulation in parkinsonian patients. Obviously, this could not

be studied in rodents, but it would be interesting to assess this possible function of STN in the monkey in the future.

**Obsessions and compulsions.** Based on the predictions from animal models, HFS of the STN for OCD could appear somewhat irrational; it was never shown to be dysfunctional in OCD, nor is it close enough to any of the structures involved to explain an effect by a simple spread of current. Nevertheless, stimulation of STN in three parkinsonian patients (Mallet et al., 2002; Fontaine et al., 2004) induced a strong improvement of their OCD. A multicenter, double-blind, sham-controlled, crossover study was therefore conducted in 17 patients to test the effects of HFS of the STN for this psychiatric disorder (Mallet et al., 2008). The boundary of the associative and limbic territories of the STN was the target (anterior and ventral), and the most ventral contact without side effects was selected for each patient. After 3 months of active stimulation, 75% of patients were improved by more than 25%. This could be explained by the key role that is given to the STN in the basal ganglia circuitry, especially regarding integration of sensorimotor, associative (cognitive), and limbic (emotional) information (Bar-Gad et al., 2003; Mallet et al., 2007). This role was partly confirmed by some of the side effects (hypomania, anxiety, dyskinesia) that were resolved by modification of stimulation parameters. Moreover, the stimulation appeared to decrease metabolism of the left anterior cingulate gyrus, as observed with positron emission tomography (PET), and reductions of the obsessions and compulsions were correlated to decreases of ventromedial prefrontal cortex metabolism (Le Jeune et al., 2010). Therefore, STN HFS, at parameters sufficiently low that they ensure the specificity of the effect, would appear to be a promising tool to help extremely severe and resistant OCD patients. Moreover, as DBS technique allows one to record neuronal activities in the structures through which pass the targeting microelectrodes, we were able to show that a number of parameters of the STN's activity were modified in OCD in comparison with PD (Welter et al., 2011) and animal data (PD models and controls) of the literature. Firing rate was lower in OCD and closer to that of animal controls, and would thus be more "normal" than in PD. On the other hand, burst activity was increased in the anterior ventromedial area, in line with a previous study (Piallat et al., 2011) and the associative and limbic functions associated to that area (Karachi et al., 2005). Furthermore, a number of burst parameters and oscillatory activities (delta and alpha bands) were correlated to symptom severity; some of these characteristics were predictive of response to treatment by DBS (Welter et al., 2011).

### NEXT STEPS?

As discrepancies exist between the functions assigned to the STN by animal studies and by clinical reports, some of the functions that do not fit with the current model of STN functions should be reconsidered. Additional functional and neuroanatomical studies are therefore needed to explain the role of the STN in OCD and impulse control (in which it seems to be of great clinical importance) (Mallet et

al., 2007, 2008; Klavir et al., 2009; Eagle and Baunez, 2010). A special focus will need to be placed on the processes related to decision-making.

### Metacognition

Among the basal ganglia, the STN seems to be involved in the control of impulsivity/inhibition of behavioral output (Frank, 2006; Eagle and Baunez, 2010). More specifically, the hyperdirect pathways from frontal cortical areas to the STN might represent the routes by which decision variables or dynamics are regulated. In Frank's model (Frank, 2006) the STN impacts on *when* a decision is made and *which* action is selected. STN HFS markedly improves the motor symptoms of Parkinson's disease, but causes cognitive side effects such as impulsivity. Frank et al. (Frank et al., 2007) showed that HFS reduces the normal ability to slow down when faced with a decision conflict, leading patients to speed up their decisions. These findings as well as a neurocomputational model of the basal ganglia (Bogacz, 2007; Frank et al., 2007; Bogacz and Larsen, 2011) suggest that the STN contributes to metacognition, that is, increasing the threshold for decision in case of conflict or ambiguous situation and thus postponing decision until enough evidence has been accumulated. The integration of motor, cognitive, and emotional processes in the basal ganglia, and especially the STN, is in favor of this concept (Parent, 1990; Parent and Hazrati, 1995a; Bar-Gad et al., 2003; Mallet et al., 2007; Yelnik, 2008; Baunez and Lardeux, 2011). Interestingly, we have collected data showing that rat STN neurons increase their activity in anticipation of future error, and so-called "oops neurons" encode errors of execution (Lardeux et al., 2009), whereas human STN neurons significantly increase their activity during the few seconds preceding compulsive checking in severe OCD patients (Burbaud et al., Submitted). These recent observations may support the involvement of STN in metacognition that remains to be investigated further.

### Recently described connections: toward new functions for STN?

Sensory information in the STN: it has been shown recently that sensory information such as visual inputs could influence the STN neuronal activity via the superior colliculus that projects directly to the STN (Coizet et al., 2009). The possible ability of STN to integrate sensory information and transfer it through the basal ganglia should lead to the future discovery of other functions to which the STN contributes.

More recently another afference to STN has been shown originating from the cerebellum (Bostan et al., 2010). It is difficult to date to assign a specific role to this connection between cerebellum and STN, but it may relate to what was mentioned previously regarding the arousal, awareness, and attentional processes.

These projections reinforce the position of the STN as a critical input structure of the basal ganglia, able to integrate sensorial, motivational, emotional, and motor-related information.

## DO KEYWORDS REPRESENT A VALID TOOL FOR CHOOSING REFERENCES ABOUT BEHAVIOR AND STN?

We would like to stress in this chapter the extreme variety of key words that are used by different clinical researchers, and even in different works addressing very similar questions based on animal models. An example can be given in the field of repetitive behaviors: a search in pubmed using the keywords <compulsion> and <subthalamic nucleus> returns 23 references including 5 reviews and 9 articles using animal models. <subthalamic nucleus> and <compulsive> returns 53 references including 15 reviews and 12 articles using animal models, these do not include all the references found with <compulsion>. <Subthalamic nucleus> and <stereotypy> returns 13 articles of which 10 used animal models. <Subthalamic nucleus> and <decision> returns 37 references with only 3 using animal models. <Subthalamic nucleus> and <impulsivity> returns 13 references including 4 reviews and 4 animal studies. <Subthalamic nucleus> and <motivation> returned 47 references including 4 reviews and 22 animal studies. It is interesting to note that given the difficulty to model obsessive-compulsive behavior in animals some authors are careful and prevent using the word compulsion to prefer perseveration, or perseverative behavior. This word is rarely used in clinical studies and therefore some clinical report can omit totally some key references in animal work. This is the case for OCD models, but could also be generalized for many psychiatric disorders that are generally difficult to model or poorly modeled in animals.

## CONCLUSION

By addressing these various questions, the present review has addressed most of the functions in which the STN has been shown to be involved, revealing a wide range of functions that are clearly far behind the restrictive motor functions that were considered until the mid-90s. The present review has also highlighted that, as far as it concerns the functions or dysfunctions of the STN, animal models have sometime provided a good support for further development or precaution in clinical treatments. In contrast, they are sometime unable to predict some of the effects observed in the patients. It is important to note that this relates mainly to psychiatric disorders, which are indeed very difficult to model or address in a satisfying manner in the animals. This last point is possibly responsible for the choice not to use specific key words when referring to some of the behavioral effects observed after STN lesion in animals, leading to the limit for clinicians in finding the references afterward in the literature.

Finally, it seems that the best correlation between animal models and clinical observations were made for motor functions. This may be again because of the difficulty to assess some of the non-motor functions in animals, but also, on the contrary, to the lack of homogeneity in the groups of patients. Clinical results can indeed be totally opposite from one study to another, as reported here for example for STN and attentional processes. The good

correlation on motor functions can also be simply due to the fact that the motor loop has been the main focus of interest for basal ganglia research that has only recently started to consider the various other loops described by Alexander in 1986. The development of surgical indication for psychiatric diseases, notably for the STN as highlighted in the present review, should lead to a better understanding of these associative and limbic loops.

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