Available online at www.sciencedirect.com
ScienceDirect
Neuroscience and Biobehavioral Reviews 32 (2008) 352–366
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
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Review

Studies of the neural mechanisms of deep brain stimulation in rodent models of Parkinson's disease ☆

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Abstract

Several rodent models of deep brain stimulation (DBS) have been developed in recent years. Electrophysiological and neurochemical studies have been performed to examine the mechanisms underlying the effects of DBS. *In vitro* studies have provided deep insights into the role of ion channels in response to brain stimulation. *In vivo* studies reveal neural responses in the context of intact neural circuits. Most importantly, recording of neural responses to behaviorally effective DBS in freely moving animals provides a direct means for examining how DBS modulates the basal ganglia thalamocortical circuits and thereby improves motor function. DBS can modulate firing rate, normalize irregular burst firing patterns and reduce low frequency oscillations associated with the Parkinsonian state. Our current efforts are focused on elucidating the mechanisms by which DBS effects on neural circuitry improve motor performance. New behavioral models and improved recording techniques will aide researchers conducting future DBS studies in a variety of behavioral modalities and enable new treatment strategies to be explored, such as closed-loop stimulations based on real time computation of ensemble neural activity.

Keywords: Deep brain stimulation; Parkinson's disease; Basal ganglia; Subthalamic nucleus; Animal models; Neurological disorders

Contents

DOI of original article: 10.1016/j.neubiorev.2007.01.002
☆This article was previously published in a regular issue of Neuroscience and Biobehavioral Reviews 31(5) pages 643–657.
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doi:10.1016/j.neubiorev.2007.09.002

1. Introduction

Deep brain stimulation (DBS) methodology has been rekindled over the last decade as an effective treatment for a variety of neurological disorders including Parkinson's diseases (PD) (Benabid, 2003). Despite its remarkable therapeutic efficacy, the mechanisms underlying the therapeutic effects of DBS have not been resolved. Animal models are essential for elucidating how DBS alleviates Parkinsonian symptoms. Unfortunately, the development of animal models of DBS has lagged behind clinical applications in the early stages of DBS research. This is partially due to the initial clinical success of treating PD with DBS (Ashkan et al., 2004).

Animal experiments with DBS were first carried out in a primate model of PD. A behavioral scoring method similar to that used in PD patients was employed to measure Parkinsonian symptoms. DBS of the subthalamic nucleus (STN) induced beneficial effects in Parkinsonian non-human primates that were similar to those observed in human PD patients (Benazzouz et al., 1993; Boraud et al., 1996; Gao et al., 1999). DBS research was expanded to include rodent models in which the electrophysiological and neurochemical responses associated with DBS could be examined in more detail. Early studies carried out in *in vitro* and in *in vivo* anesthetized rodent preparations provided detailed information about neural responses to high frequency stimulation (HFS) that mimics clinically applied DBS. However studies of anesthetized models obviously lack behavioral corroboration of the DBS effect, and these non-behavioral studies have produced considerable variability in results depending upon the stimulation parameters applied, and preparation methodology used. The subsequent establishment of DBS models in behaving rats with nigrostriatal dopamine (DA) depletion enabled DBS effects to be studied in a model that mimics clinical conditions. This review will discuss recent developments and advances in DBS basic research employing rodent models.

2. Rodent models of DBS

Rodent models have been widely used over the last three decades for PD research. The commonly used unilateral 6-hydroxydopamine (6-OHDA) nigrostriatal lesion model can produce in rat the major symptoms of PD including akinesia, posture abnormality, tremor and dyskinesia (Cenci et al., 2002). Many of these motor deficits can be easily scored to obtain quantitative measures of motor deficits, which can then be correlated with the degree of DA depletion (Schallert and Tillerson, 2000; Montoya et al., 1991; Kirik et al., 1998). There is a debate about how accurately such a hemi-Parkinsonian model duplicates the clinical conditions of PD. Nevertheless, the existence of an intact side in the model can serve as a within-subject control, which has clear advantages for evaluating the neurochemical, electrophysiological and behavioral changes induced by unilateral DA depletion.

Rat models of PD can be used to study the effects produced by DBS and ultimately the mechanism mediating the therapeutic benefits of DBS. It has been demonstrated in such rodent models that implanting microelectrodes in the STN and applying stimulation parameters similar to those used in human patients can improve motor activity (Chang et al., 2003; Darbaky et al., 2003; Shi et al., 2004; Temel, et al., 2005). Electrodes used in human patients and experimental animals have different sizes and shapes. Electrodes used in the rat are smaller than those used in human patients. One concern is that different components of the nervous system might be activated by DBS in human and animal studies, since the electrodes used in animal experiment have high current density and thus are more likely to activate nerve fibers than cell bodies (Ashby, 2000; Lozano et al., 2002). Recent studies have characterized current density, electric field distribution, electrochemical responses and electrode geometric factors during DBS in both human and animal experiments (McIntyre and Grill, 1999, 2001; Kuncel and Grill, 2004; Gimsa et al., 2005, 2006; Harnack et al., 2004; McIntyre et al., 2004). Finite element analysis revealed non-uniform current density in conical microelectrodes with sharp tips (1.5 μm tip radius). Current density was concentrated at the tip of the microelectrode and at the electrode insulation interface. On the other hand, electrodes with a relatively large surface area ($>30\,\mu m$ in diameter) can achieve nearly uniform current density distribution along the surface of the electrode (McIntyre and Grill, 2001). In many cases, stimulation parameters have to be determined by considering a variety factors such as electrode geometry, medium components, electrode placements, and electrochemical responses (Kuncel and Grill, 2004; Gimsa et al., 2005, 2006). By carefully selecting the electrode metal material (platinum/iridium instead of stainless steel) and current intensity, a long term, safe stimulation protocol can be achieved in rats if the charge density is kept below $30\,\mu C/cm^2$/phase, the recommended threshold for the Medtronic electrode used in human patients (Harnack et al., 2004). Thus it appears to be feasible to use a rat model of PD to study the effects of DBS. Calculations related to excitation or inhibition of neuronal elements

surrounding the stimulus are clearly of value. Our view is that future studies will need to employ advanced new methods for artifact suppression and recording from populations of neurons surrounding the stimulus site to empirically determine precisely what has been activated.

2.1. Treadmill locomotion model

Treadmill locomotion tests have been used to evaluate sensorimotor function under normal and pathological conditions (West, 1998; Chapin and Woodward, 1982). Treadmill experiments have also been employed to assess DA depletion-induced motor deficits. Early studies used an electric tail-shock to assess akinesia induced by unilateral DA depletion. In such experiments, rats run on the treadmill at a fast pace and an electric shock is delivered to the tail whenever they failed to keep up with the treadmill speed and are pushed back to the end of treadmill belt. The number of electric shocks delivered can then be used as a measure of the degree of motor deficit following DA depletion (Hattori et al., 1993). Considerable stress is associated with this test because of the high running speed and the frequent electric shocks.

A less stressful version of the treadmill test was recently developed in which rats were only required to maintain a moderate walking speed (Chang et al., 2003, 2006). Neurologically intact rats normally start walking once the treadmill begins to move and easily maintain a position at the front of the chamber. On the contrary, 6-OHDA-lesioned rats' initiation of walking is delayed and because they struggle to catch up with and follow the treadmill movement, they often walk at the back of the chamber. In this test, details of swing and stance times of the forelimbs can be measured during step cycles. The swing time (when the forelimb was moving through the air) was found to be decreased significantly in both forelimbs of 6-OHDA-lesioned rats, resulting in generation of small, quick steps (Chang et al., 2006). The stance time (when the forelimb was in contact with floor), on the other hand, was found to be increased significantly only in the "good" limbs ipsilateral to the lesion. The increases in stance time in the good limbs reflected longer steps made by the good limbs to compensate for the smaller steps made by the bad limbs. This modified treadmill paradigm enables these kinetic features of locomotion to be examined precisely in order to identify and characterize DA depletion-induced motor deficits during normal walking behavior (Fig. 1).

This quantifiable treadmill model of PD is well suited for DBS studies because improvements following stimulation can readily be determined by the position attained by the rat on the treadmill within the chamber. HFS of either the STN or the substantia nigra pars reticulata (SNr) significantly improved treadmill walking patterns in this behavioral model and brought swing and stance times to control levels (Chang et al., 2003; Shi et al., 2006). As shown in Fig. 1B, both swing and stance times were normalized during behaviorally effective DBS, which resulted in a restoration of normal treadmill locomotion patterns. The stimulation intensity that was effective for improving treadmill locomotion performance did not induce any side effects, indicating that the effects of DBS were specific for improving Parkinsonian symptoms by enabling intended movement. Therapeutic effects of DBS were only found when the tips of the electrodes were located in the vicinity of STN region, highlighting the anatomic specificity in the rat model of DBS (Chang et al., 2003; Shi et al., 2004).

This treadmill model employs a normal walking pace and mimics the symptoms observed in Parkinsonian patients. The absence of movement directly evoked by

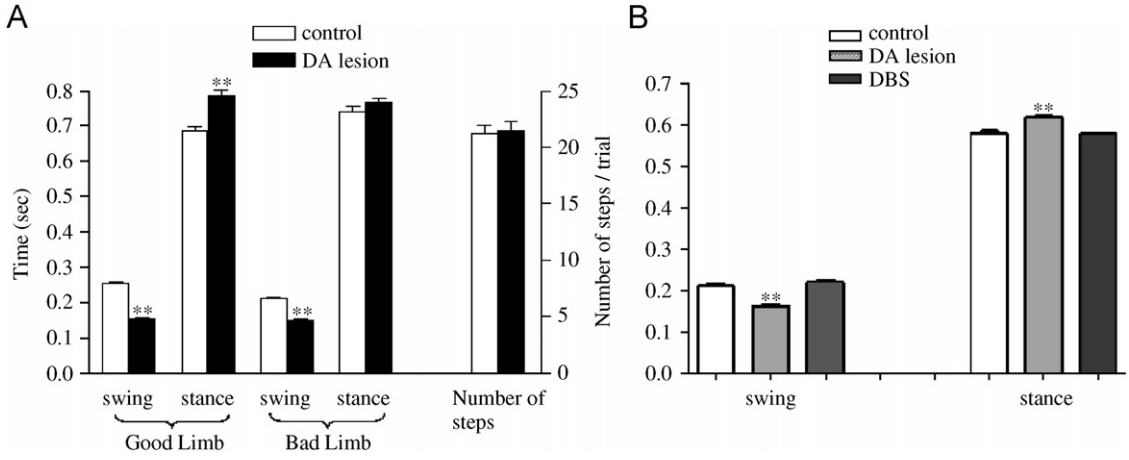

Fig. 1. Changes in swing and stance times and number of steps after unilateral 6-OHDA lesion and STN DBS. Off-line video analysis was performed in right forelimbs during treadmill walking. (A) The swing time was significantly reduced in both the good (ipsilateral to lesion) and the bad (contralateral to lesion) limbs. Stance time was significantly increased only in the good limbs. As a result, the total number of steps per trial was not changed by the lesion (**$p<0.01$, Student's t-test). (B) Effects of STN DBS on treadmill locomotion. Locomotor activity was assessed by analysis of swing and stance times. Unilateral 6-OHDA lesioned rats exhibited akinesia during treadmill locomotion. A significant decrease in swing time and increase in stance time were observed in the lesioned condition. DBS restored swing and stance times to control levels. (**$p<0.01$, ANOVA). Adapted with permission from Chang et al. (2006), and Shi et al. (2006).

stimulation alone with the DBS treatment suggests that DBS does not directly activate movements *per se*, but rather serves an enabling function to facilitate intended movement. The effects of DBS can be quantified readily in this model, making it a useful tool for multi-disciplinary neuroscience research examining the neural mechanisms of DBS.

2.2. Limb use asymmetry model

The limb use asymmetry test was developed recently to test motor function in unilateral 6-OHDA lesioned rats and has been employed by many laboratories studying PD (Schallert et al., 2000; Lundblad et al., 2002; Shi et al., 2004; Mehta and Chesselet, 2005). In this test a rat is placed in a cylindrical chamber and allowed to behave spontaneously. Rats normally stand up on their hind limbs leaning on the inside of the plexiglass cylinder and then move from side to side by repositioning the forelimbs. A normal rat uses both forelimbs with roughly equal frequency to touch the wall of cylinder, whereas a unilateral 6-OHDA lesioned rat predominantly uses the good limb ipsilateral to the lesioned side to touch the wall and support its body weight.

The limb use asymmetry test has several advantages in the assessment of the effectiveness of DBS. On a conceptual level, the nature of the motor manifestation being tested is clear and simple. The postural support and weight-shifting movements observed are identical to those typically performed by a rat in its home cage, and are examined without experimenter handling. The test is relatively objective, quick and simple to carry out; and it does not require animal training, aversive motivation, or food deprivation, which are known to influence function in Parkinsonian models. The behavior is stable chronically and easy to quantify. The test is very sensitive even to partial DA depletion (Schallert and Tillerson, 2000), and importantly, the absence of a drug challenge eliminates confounding factors for interpreting the experimental results.

The limb use asymmetry test may also have clinical relevance. The forelimbs are used to initiate movements that require weight shifting, much like legs are used by humans when they walk. Difficulty in initiating steps from a standing posture or regaining center of gravity, is one of the primary signs of extensive degeneration of DAergic neurons in the substantia nigra (Dunnett and Robbins, 1992; Langston, 1990). Decreased rearing activity observed after unilateral DA depletion is more likely attributed to a movement-related impairment rather than to habituation to the experimental environment or a long-lasting anesthetic effect since sham control animals do not exhibit significant changes in rearing activity.

We have tested the effects of STN DBS in this model and found that HFS of the STN has benefits similar to the therapeutic effects of DBS observed in Parkinsonian patients. Namely, during DBS, rearing activity in unilaterally lesioned rats was no longer significantly impaired relative to the control condition and limb use asymmetry was reversed. The benefits of DBS were maintained throughout the experimental sessions (8–15 min) without causing any abnormal side effects. The beneficial effects of DBS on limb use seem to be specific to motor deficits induced by DA depletion since STN DBS in the intact animal did not influence limb use asymmetry or affect rearing activity (Shi et al., 2004).

2.3. Reaction time model

Simple reaction time tests have been used to document sensorimotor functional deficits in Parkinsonian patients. The sensorimotor performance deficits have been attributed to attentional deficits or motor impairments or a combination of the two. (Evarts et al., 1981; Rafal et al., 1987; Bloxham et al., 1987; Mazzucchi et al., 1993; Gauntlett-Gilbert and Brown, 1998; Pullman et al., 1988). To further explore the neural mechanisms underlying these impairments, an experimental animal model has been developed using a reaction time test (RTt), and RTt deficits have been reported in rats with nigrostriatal DA lesions (Amalric and Koob, 1987; Amalric et al., 1995; Brown and Robbins, 1991). Extensive evidence indicates that correct execution of the RTt requires the coordination of the entire basal ganglia thalamocortical circuitry (Amalric et al., 1994; Baunez and Amalric, 1996; Baunez and Robbins, 1997). Among the structures within the circuit, the STN has received considerable attention due to its pivotal position; it is connected to the cortex, brain stem structures and the indirect basal ganglia pathway. Rats with STN lesions show an increase in the number of early, anticipatory responses in the RTt prior to the go signal. This effect can be attributed to a failure of response inhibition, since the STN normally augments basal ganglia inhibitory output via the SNr and the endopedencular nucleus (Baunez and Robbins, 1997; Phillips and Brown, 2000). Indeed, a blockade of NMDA receptors in the SNr that eliminates most of the STN excitatory input has been shown to mimic the effects of an STN lesion in the RTt (Baunez and Amalric, 1996). On the other hand, in rats with a striatal DA lesion, concurrent lesions of the STN attenuated the DA lesion-induced prolongation of the reaction time response (Phillips and Brown, 1999; Baunez et al., 1995; Baunez and Robbins, 1999).

The effect of STN DBS on performance in a choice RTt of normal and DA depleted rats has been examined. In one such test, rats were required to hold position within a nose-poke device while waiting for a cue (a tone or light). When the cue was presented, the rats needed to withdraw their noses from the nose-poke slot within a short period of time (the reaction time) and then either execute another nose-poke or lever-press (in the right or left side depending on the cue) in order to obtain a reward. The magnitude of the effect of the STN DBS treatment was dependent upon the degree of DA lesioning. While DBS did not alter the number of responses, it did attenuate contralateral neglect, as failure to respond to cues presented opposite to the lesion, in some mildly DA lesioned animals (Darbaky et al., 2003).

Another study revealed that in partial bilateral DA lesioned rats, bilateral STN DBS reduced the number of premature responses (release of the panel before the cue onset) at stimulation intensity as low as 3 μA. Reaction time (the latency between the cue onset and panel release) and motor time (the latency between panel release and lever-press) that had been prolonged by DA depletion were reduced when 30 μA DBS was applied (Temel et al., 2005). The authors suggested that DBS of different intensities could differentially modulate cognitive and motor functions within the basal ganglia thalamocortical circuits and that the STN appears to play a pivotal role in regulating both cognitive and motor functions.

2.4. DBS effects on sensorimotor integration

Though PD is considered primarily a motor disorder, a converging evidence has pointed to the involvement of sensory deficits in PD. Sensory feedback is an important component of the complex motor planning required for normal motor actions. Inputs from different sensory modalities are integrated into the motor program to initiate and execute the motor action according to the environmental conditions. Thus abnormal sensory processing may partially account for motor impairments associated with PD and dyskinesia (Abbruzzese and Berardelli, 2003; O'Suilleabhain et al., 2001).

Sensory neglect is an early sign of DA depletion in a rodent model of PD in which hemi-Parkinsonian rats fail to respond to touches applied to the side of the body contralateral to the DA lesion (Marshall et al., 1971). Whisker stimulation-evoked c-fos expression is attenuated in the barrel cortex following nigrostriatal DA depletion (Steiner and Kitai, 2001). Deficits in other sensory modalities have also been demonstrated in animal models of PD and in human patients. Using a classic conditioning task, Aosaki et al. (1994) reported a loss of tone-induced striatal neural responses in monkeys following unilateral striatal DA lesioning. Similar losses of tone responses were found in several basal ganglia regions ipsilateral to a DA lesion during a treadmill locomotion task (Chang et al., 2006). Visual neglect has been observed in an animal model of PD (Carli et al., 1989; Miyashita et al., 1995), and a mismatch of proprioceptive and visual inputs was reported in Parkinsonian patients (Demirci et al., 1997). Proprioceptive input was disrupted in both Parkinsonian patients and in an animal model of PD. Escola et al. (2002) found that motor cortical neurons lost their specificity in coding joint movements in 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys; instead of responding to one joint and one direction of movement, motor cortical neurons in the lesioned animals responded to movements of multiple joints and to several directions of movement. Furthermore, PD patients have been reported to exhibit impaired performance on kinesthesia (awareness of limb position) tests (Jobst et al., 1997; Maschke et al., 2003).

If impairment of sensory processing contributes to PD motor symptoms, then sensory cues should be able to improve motor performance. Consistent with this prediction, it has been shown that visual cues marked on the floor helped Parkinsonian patients to maintain their stride length (Morris et al., 1996). Likewise, a rhythmic auditory stimulation significantly improved gait velocity, cadence, and stride length in PD patients (McIntosh et al., 1997), and in a writing test, both visual cues and auditory reminders prevented micrographia (letters getting smaller during the writing) in Parkinsonian patients (Oliveira et al., 1997).

To test the hypothesis that DBS can regulate sensorimotor integration processing in Parkinsonian conditions, we have developed a whisker stimulation test to study the effects of DBS on the sensorimotor integration process in unilateral DA depleted rats. A preliminary study showed that rats could be trained to orient to the whisker stimulation. To facilitate the orienting response, rats were food-deprived for 24 h before the experiment. A probe was attached to a solenoid so that a key stroke generated 10-mm vertical movement of the probe. To reinforce the response to the whisker touching, a food pellet was attached at the tip of probe. When a rat's whisker was touched by the probe, the rat turned abruptly to the probe to grab the food pellet. Neurologically intact rats were able to obtain the food pellet within 0.5 s of whisker touching. Meanwhile unilateral DA-depleted rats showed significantly delayed or absent responses to stimulation of a whisker contralateral to the lesion (bad side), with normal responses to stimulation of an ipsilateral whisker (good side).

Our preliminary experiments employing the whisker stimulation test indicate that STN DBS can significantly improve reaction time following stimulation of a whisker contralateral to the lesion. In addition, the number of responding trials increased from $<40\%$ of total trials on the bad side to $>70\%$ during DBS (100% response rate observed on good side). These findings provide evidence that DBS can restore motor responses to sensory stimulation. However, it is not clear to what extent the motor vs. sensory process is involved in such a behavioral deficit or its DBS-induced recovery. We are currently conducting an electrophysiological study aimed at dissecting sensory vs. motor components involved in DBS. Preliminary results suggest that STN DBS can regulate the sensory gating process in the cortical basal ganglia system by recovering sensory processes that may contribute to the normalization of sensorimotor integration. Our hypothesis is that the deficit may involve a disturbance throughout the cortical striatal system as signals cycle and spread through a circuit deficient in dopamine. Distributed recording will be needed to clarify the persistent altered patterns.

2.5. Other behavioral models

DBS has also been tested in behavioral models induced by manipulation of DA neurotransmission. STN DBS has been reported to reverse neuroleptic-induced catalepsy

following transient inactivation of DA receptors (Darbaky et al., 2003; Degos et al., 2005). STN DBS has also been reported to reduce turning induced by injection of the potent DAergic receptor agonist apomorphine in unilateral 6-OHDA lesioned rats (Darbaky et al., 2003). However, the stimulation parameters that improved performance in the treadmill locomotion and cylinder tests in our laboratory could not produce a reduction in apomorphine-induced turning (Chang et al., 2003; Shi et al., 2004). DA receptor agonism-induced rotation is a classical model for evaluating the degree of DA depletion following a unilateral 6-OHDA lesion (Ungerstedt, 1971; Schwarting and Huston, 1996). However, it is not a suitable model with which to test potential PD therapeutic interventions because it involves abnormal movement produced by a mechanism distinct from the mechanism that produces the typical Parkinsonian bradykinesia. Instead, activation of supersensitive DA receptors may induce a form of dyskinesia that is similar to that observed in patients receiving long term DAergic supplementation such as L-Dopa. Furthermore, vigorous stereotyped behaviors induced by DA agonists could potentially mask side effects induced by DBS administered at an intensity that is above the therapeutic range. Such side effects include turning and stretching of the forelimbs, which may at times counteract or block drug-induced rotations.

3. Mechanism of DBS

A basic model for the occurrence of Parkinson's motor symptoms is that activity in the STN becomes elevated in the absence of adequate DA, and that this leads to increased inhibitory output from the SNr and globus pallidus internal (GPi). This effect has been postulated to lead to enhanced inhibition within the thalamus. This inhibition in turn may suppress or block the spatial temporal patterns of activation that activate motor areas employed to generate intentional movement (Delong, 1990; Albin et al., 1989). This now classical model has provided a basic hypothesis driving much research over the past two decades. The prediction is that local inhibition of STN neurons produced by DBS should have an effect similar to an STN lesion. Inactivation leading to lower overall activity within the STN is predicted to decrease the excitatory drive of the SNr/GPi, release the inhibition of thalamus and thus alleviate Parkinsonian symptoms. Considerable experimental effort has been directed to test this classical model.

As part of the indirect pathway, the STN is the only structure in the basal ganglia containing excitatory glutamatergic neurons that project to the GPi and the SNr, the basal ganglia output sites. The STN also send projections to the striatum, globus pallidus external (GPe) and some brain stem areas (Hamani et al., 2004). The STN receives GABAergic input from the GPe and glutamatergic input from the cortex. DAergic neurons in the SN pars compacta (SNc) also send a moderate projection to the STN. With such a widespread set of interconnections, it is clear that stimulation of STN could have an impact on many interconnected structures in the brain.

A basic task has been to determine whether direct stimulation within the STN yields excitation or inhibition of STN neurons, and what the impact of such stimulation on other brain regions directly or indirectly connected to the STN may be, especially the basal ganglia output sites. In rodents, DBS studies have been performed both *in vitro* and *in vivo* preparations. The latter have been carried out both in anesthetized and in behaving animals. These different approaches address a variety of aspects of DBS actions and can be complementary in resolving the mechanism underlying the therapeutic effects of DBS.

3.1. In vitro studies

Electrophysiological studies using *in vitro* slice preparations provide detailed information about the effects of DBS at the membrane level. Studies have shown that HFS of the STN at a frequency similar to that used *in vivo* to treat PD, significantly inhibited STN neurons in the slice preparation (Beurrier et al., 2001). The authors argued that this inhibition was more likely to be the result of an alteration in the intrinsic voltage gated currents rather than an alteration of synaptic transmission since pharmacological block of both GABA and glutamate receptors had no effect on the inhibition.

A similar finding was reported in another study using a subthreshold stimulation current that did not evoke action potentials. HFS of the STN induced an initial depolarization of STN cells that triggered an increase in firing rate to a level as high as 300 Hz; this was followed by burst activity and shortly after (25 s), a total shutting down of STN cells, even with a sustained depolarization of membrane potential (Magarinos-Ascone et al., 2002). The authors suggested that this sustained inhibition can be attributed to an inactivation of Na^+ channels mediated action potentials rather than presynaptic depression caused by the HFS. These findings are consistent with the view that local inhibition of the STN neurons may account for the therapeutic effects of DBS observed in Parkinsonian patients.

Stimulation frequency- and duration-dependent STN neural responses were found in an intracellular slice study (Lee et al., 2003). In this study, a similar biphasic response (an initial increase in firing rate followed by inhibition) was observed during HFS of the STN. The maximum increase in firing rate occurred in the initial phase of stimulation at 100–140 Hz, while a further increase in stimulation frequency to 200 Hz suppressed the neural responses. Furthermore, the period of inhibition was correlated with the duration of stimulation: the longer the HFS, the longer the post stimulation inhibition. This phenomenon was interpreted as resulting from HFS-induced depletion of glutamatergic neural transmission in the STN.

Local inhibition of STN neurons by HFS, whatever the mechanism, may act similar to an STN lesion to inactivate the STN and thus alleviate Parkinsonian symptoms. Such an STN inactivation hypothesis is in accordance with the classical model described above of basal ganglia thalamocortical pathways, which predicts that there will be an increase in the activity of STN neurons after DA depletion (Delong, 1990; Albin et al., 1989). However, findings from other *in vitro* studies have challenged the concept of local inhibition. Garcia et al. (2003, 2005) reported that HFS of the STN abolished spontaneous activity of STN neurons, but nevertheless evoked recurrent burst activity with each spike time-locked to the stimulation pulses. In contrast to the transient initial excitation found in other studies (Magarinos-Ascone et al., 2002; Lee et al., 2003), this evoked activity lasted for more than 60 min. As with the inhibitory responses observed in other studies, this evoked burst activity was attributed to the direct action of HFS on the cell membrane, since it was not blocked by GABAergic or glutamatergic receptor antagonists. Burst firing activity during HFS may be mediated by a resurgent Na^+ current. In experiments examining dynamic firing patterns in dissociated rat STN neurons, Do and Bean (2003) found that a resurgent Na^+ current, together with a persistent Na^+ current, may be responsible for the generation of high tonic firing and burst firing patterns by HFS. These two Na^+ currents were under the regulation of a slow inactivation process to maintain a constant firing rate. Another study, however, reported that HFS caused a short term potentiation of activity within the STN in the presence of a GABAergic receptor antagonist, and suggested that presynaptic release of glutamate may play a significant role (Shen et al., 2003).

The inconsistency among these results may be due to the specific stimulation parameters used in the experiments. Subthreshold 1-μA currents were used in the study demonstrating inhibitory effects (Magarinos-Ascone et al., 2002), whereas much higher currents of 0.5–3 mA were used in the studies showing evoked responses (Garcia et al., 2003, 2005). Though it is difficult to compare *in vitro* studies directly with *in vivo* behavioral experiments, the current intensity used in these *in vitro* studies are not in the same range of the stimulation currents (50–200 μA) that produce beneficial behavioral effects in rodent models of PD (Chang et al., 2003; Degos et al., 2005; Shi et al., 2004; Darbaky et al., 2003). Since many connections are severed in the *in vitro* preparations, and behavioral verification is not possible, caution is required when interpreting the results.

3.2. *In vivo studies in anesthetized animals*

Similar to some of the *in vitro* studies discussed above, Benazzouz et al. (2000a) found that HFS of the STN reduced activity of STN neurons in the vicinity of the stimulation electrode tip in anesthetized rats. Furthermore, this STN inhibition was coincident with inhibition of the SNr and excitation of the globus pallidus (GP), SNc and ventrolateral thalamic nucleus (VL) (Benazzouz et al., 1995, 2000a, b; Tai et al., 2003). This response pattern fits very well with the classical model of basal ganglia thalamocortical circuitry: reduced activity in the STN results in decreased activity in the SNr due to reduced glutamatergic signaling to the SNr. Inhibition of the SNr in turn is postulated to disinhibit the VL and thus enhance the feedback signals to the cortex (Delong 1990; Albin et al., 1989; Alexander et al., 1990). However, several caveats need to be taken into account when evaluating these results. Firstly, the stimulation parameters, though mimicking very closely those used in the clinic to treat PD, have not been tested for improving Parkinsonian syndromes in animal models. Secondly, anesthesia can alter neural responses in the basal ganglia (Pan and Walters, 1988; West et al., 1990), which confounds the interpretation of these findings. Thirdly, the responses are not observed during DBS (with the exception of Tai et al., 2003) when the therapeutic effect manifests, but are observed *after* termination of DBS to avoid stimulation artifacts, a common problem in DBS studies.

Recent studies by other groups have focused on the effects of STN DBS on SNr neural activity in anesthetized rats using stimulation parameters shown in behaving animals to ease catalepsy induced by DA receptor antagonism (Maurice et al., 2003; Degos et al., 2005). In contrast to the inhibitory responses commonly observed after STN DBS, stimulation intensity-dependent SNr neural responses were found during HFS of the STN in these studies. Low intensity stimulation (<4 V) reduced SNr firing, whereas high intensity stimulation increased the firing rate during HFS (Fig. 2). The inhibition caused by low intensity stimulation is likely mediated by GABAergic receptors as evidenced by the observation that application of the GABAergic antagonist bicuculline blocked the inhibition. On the other hand, the excitation caused by high intensity stimulation is likely the result of activating excitatory subthalamonigral projections or antidromic activation of SNr neurons caused by stimulation of SNr fibers of passage. During high intensity stimulation-induced excitation of the SNr, spontaneous spikes were suppressed. Furthermore, cortical stimulation-induced SNr action potentials were differentially modulated by HFS of the STN. That is, later responses representing activation of the indirect subthalamonigral pathways were greatly reduced relative to early responses representing activation of striatonigral direct pathways.

The SNr neural responses during DBS that exert beneficial behavioral effects have not been clearly identified. To address this critical issue, Degos et al. recently conducted a study that included DBS experiments in both awake behaving animals and in anesthetized animals (2005). They first tested the effect of STN DBS on DAergic antagonism-induced catalepsy and then applied a similar stimulation protocol to anesthetized animals and recorded the neural responses in the SNr. Rather than recording SNr

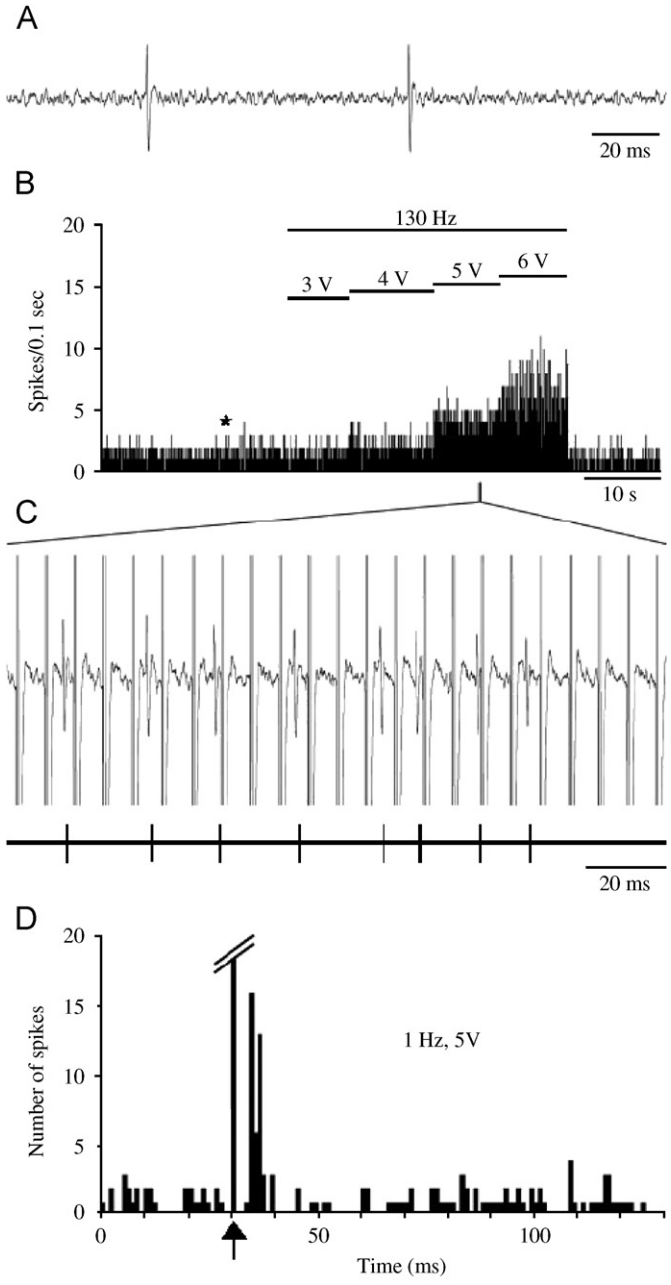

Fig. 2. Excitatory effects of STN high frequency stimulation on the activity of an SNr cell: (A) activity trace recorded before STN high frequency stimulation taken at the time indicated by the star in B; (B) rate histogram illustrating the evoked increase of firing of a SNr cell during STN high frequency stimulating (130 Hz) with increasing intensities (3,4,5, and 6 V); horizontal lines indicate the time of application of STN stimulation with the corresponding intensity: note that the excitatory effect was elicited only during application of STN stimulation at high intensity; (C) magnified view of the recording (top trace) and of the event channel (bottom trace), confirming that only spikes were sampled. (D) Peristimulus time histogram illustrating the excitatory responses evoked in the same SNr cell by STN stimulation at 1 Hz and 5 V; arrow indicates the time of the stimulation application. Maurice et al. (2003) Copyright 2003 by Society for Neuroscience.

neural responses to HFS of the STN in intact rats as had been done previously (Maurice et al., 2003), Degos et al. examined the neural responses in a DA depleted condition. Furthermore, the stimulation parameter that induced beneficial behavioral effects was used to test the neural responses in the SNr. The authors found heterogeneous neural responses in the SNr during STN DBS; both inhibitory and excitatory SNr neural responses were detected with an overall increase in firing rate. Thus in light of the previous demonstrations of stimulation intensity-dependent neural responses (Maurice et al., 2003), behaviorally effective DBS seems to be in the middle of the stimulation intensity spectrum. Moreover, these results suggest that effects on rate change alone in the SNr may not fully account for the beneficial effects of DBS. In particular, neuronal signaling may be regulated by changes in firing patterns. For example, the induction of catalepsy with a neuroleptic treatment was shown to be associated with an increase in irregular burst spikes, and DBS applied at the parameters that alleviate catalepsy normalized neural firing patterns in the SNr and restored normal information transmission from the cerebral cortex that had been interrupted by the neuroleptic treatment (Degos et al., 2005). These new results do not support the classic view that an increase in SNr activity is a primary deficit.

3.3. *In vivo studies in awake behaving animals*

Elucidating the neural activity changes that underlie the therapeutic effects of DBS on Parkinsonian symptoms can only be achieved with electrophysiological studies that are conducted during behaviorally effective DBS in freely moving animals. Such studies have been carried out in the both primates and rodents (Hashimoto et al., 2003; Meissner et al., 2005; Shi et al., 2006). We have simultaneously recorded neural activity in several basal ganglia regions during behaviorally effective STN DBS in rodent models of PD. In the treadmill locomotion task, intermittent HFS of the STN (3-s on, 2-s off stimulation cycle over a 20-s treadmill walking phase) significantly improved treadmill-walking patterns. We found overwhelming inhibitory responses in the vicinity of the STN stimulation site during DBS (Shi et al., 2006). Interestingly, the inhibition spread to the contralateral STN, which may replicate the mechanism by which unilateral DBS can have bilateral effects in PD patients (Bastian et al., 2003; Linazasoro et al., 2003; Germano et al., 2004; Chung et al., 2006). Similar inhibitory responses were also found in the STN in awake patients with PD (Filali et al., 2004). It is worth noting that due to the existence of the stimulation artifact, we cannot rule out at present the possibility that STN neurons may be directly activated by HFS, as demonstrated in *in vitro* studies (Garcia et al., 2003, 2005). However, local injection of GABAergic receptor agonists or lidocaine into the STN has been found, like DBS, to improve Parkinsonian symptoms in human patients (Levy et al., 2001), which supports the notion that local inhibition is at least partially responsible for the therapeutic benefits of DBS.

Neural response patterns in the basal ganglia output sites during behaviorally effective DBS have great significance for our understanding of the mechanism of DBS. As discussed above, a lasting inhibition of GPi neural activity was observed in anesthetized rats (Benazzouz et al., 1995; Tai et al., 2003), whereas a mixture of responses was found in SNr neurons in anesthetized rats using behaviorally relevant HFS (Degos, 2005). Moreover, in a primate model of PD, a predominent increase in firing rate was found during behaviorally effective DBS (Hashimoto et al., 2003). In our treadmill-walking model, we also found a mixture of responses in SNr neurons during behaviorally effective STN DBS. Because the numbers of SNr cells that exhibited excitatory and inhibitory responses were nearly equal, the mean firing rate did not change significantly during DBS (Shi et al., 2006).

Overall, the complex results obtained from behaviorally relevant DBS are difficult to fit into the classical model of basal ganglia thalamocortical circuitry. Indeed both Hashimoto's and Degos' findings of reduced burst firing in the GPi and SNr suggest that regulation of firing patterns may play an important role in mediating the effects of DBS. Furthermore, reduced burst firing patterns were also found in the STN stimulation site and in the GP in our treadmill study (Shi et al., 2006). To avoid stimulation artifacts, we calculated burst-firing patterns during the 2-s stimulation off period of the stimulation cycle during which the behavioral effect of DBS persisted. A reduced burst-firing rate was found in the STN and GP, but not in the SNr, during this stimulation off period (Fig. 3). The failure to detect changes in burst firing in the SNr during the brief 2-s stimulation off period does not rule out the possibility that burst firing may be reduced during the 3-s HFS period as Degos et al. found. The lingering effect of DBS on burst-firing patterns in the STN and GP may be due to a stronger impact of DBS upon these two areas, as STN neurons are in close proximity to the stimulation target, and GP neurons may be antidromically activated by STN stimulation.

Recent studies indicate that abnormal synchronized oscillation may take place in Parkinsonian conditions as a result of a short circuit between cells within the normally segregated, parallel basal ganglia thalamocortical pathways. A feedback circuit between the STN and GP may serve as an intrinsic pacemaker to generate low frequency oscillation (0.4–1.8 Hz). In this circuit, inhibitory GP input is required to recruit rebound excitation of STN neurons and sustain oscillatory activity (Plenz and Kitai, 1999). DAergic transmission and cortical inputs also play significant roles in generating low frequency oscillation in the STN–GP network. DA depletion has been shown in anesthetized rats to result in low frequency oscillation in the GP that is synchronized with normal cortical–subthalamic oscillation that exists in the intact condition. Furthermore, disconnection of cortical input eliminated the STN–GP oscillatory activity; suggesting neural firing pattern in the cortical basal ganglia played a significant role in coding information (Magill et al., 2001; Bevan et al., 2002). Synchronized bursting was found in the primary motor cortex in monkeys treated with MPTP (Goldberg et al., 2002, 2004). A β band cortical oscillation (15–30 Hz) synchronized with activity in the STN has been detected in Parkinsonian rats by local field potential and cortical electroencephalogram recordings (Sharott et al., 2005). Similar findings have been reported in human patients with PD (Fogelson et al., 2005a, b; Levy et al., 2002). This β band oscillation disappeared after L-dopa or DBS treatments and has been posited to be an 'antikinetic rhythm' in the cortical basal ganglia system that may underlie Parkinsonian symptoms (Silberstein et al., 2005; Brown and Williams, 2005). Abnormal oscillatory activity in STN neurons was also reduced by behaviorally effective STN DBS in a primate model of PD (Meissener et al., 2005). These findings of emergent oscillatory activity in PD and

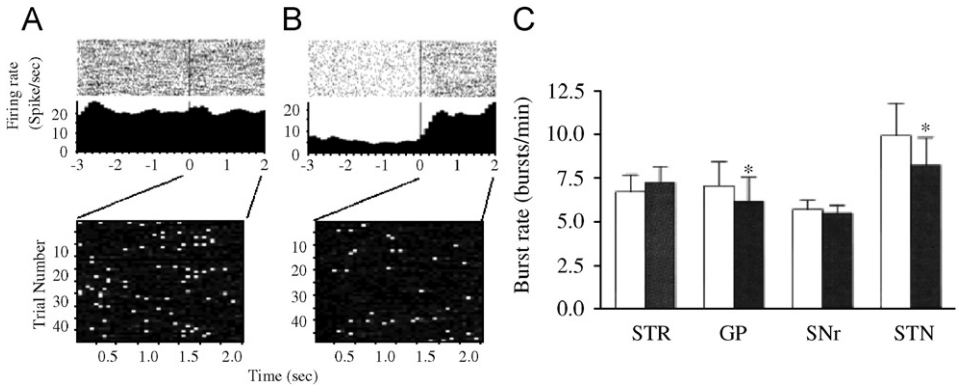

Fig. 3. Decreased burst firing during the 2-s stimulation-off period in the STN stimulation site: (A) firing rate (top panel) and burst activity (bottom panel) in control condition without DBS. The plot was made using events created at a rate of 130/s (same as DBS frequency) as reference. Two-second segments were selected to calculate burst activity (marked by bright spots); (B) neural activity and burst firing of the same neuron during behaviorally effective HFS. The firing rate was substantially reduced during the 3-s stimulation-on period and returned to control level during 2-s stimulation-off period (top panel). The occurrence of burst spikes (bright spots) was reduced substantially during the 2-s stimulation-off period (bottom panel) in comparison with the control condition; (C) changes in burst firing in different regions of the BG during behaviorally effective DBS. Significant decreases in burst firing rate were found in the GP and STN during the 2-s stimulation off period. Adapted with permission from Shi et al. (2006).

PD models are consistent with the alternate hypothesis that the therapeutic effects of DBS may be the result of desynchronization, and further suggest that it may be worthwhile to pursue different approaches to DBS therapy, such as a double pulse stimulation to desynchronize the local network (Tass, 2001, 2003; Rubin and Terman, 2004; Garcia et al., 2005).

3.4. Neurochemical mechanisms of DBS

It has been suggested that the therapeutic effects of DBS may be mediated by augmenting DA release from surviving DAergic cells. This hypothesis is based on the finding that HFS of the STN increased DA metabolism and release. Early reports showed that HFS of the STN increased 3,4-dihydroxyphenylacetic and homovanillic acid, major DA metabolic products, in the striatum in 6-OHDA lesioned rats. DA content, however, was not changed by HFS of the STN in either intact or 6-OHDA lesioned animals (Meissner et al., 2001). Other studies have reported increases in striatal DA efflux in intact rats and to a lesser extent in 6-OHDA lesioned rats (Bruet et al., 2001; Meissner et al., 2003; Lee et al., 2006). The significance of such an increase in DA metabolism and release in animal models has been questioned because DBS is applied to advanced Parkinsonian patients, who have suffered a substantial loss of DAergic neurons, and because clinical experiments utilizing PET imaging have failed to demonstrate changes in striatal DA release in Parkinsonian patients (Abosch et al., 2003; Hilker et al., 2003; Thobois et al., 2003). Thus the clinical data available thus far indicate that it is unlikely that DA transmission plays a significant role in mediating the effects of DBS.

On the other hand, recent studies have shown that HFS of the STN can modulate glutamatergic and GABAergic transmission in the basal ganglia and these findings are consistent with the possibility that the therapeutic effects of DBS may be mediated, perhaps in part, via effects on glutamatergic and/or GABAergic transmission. In accordance with the electrophysiological study showing an increase in firing rate of GPi neurons during DBS in Parkinsonian monkeys (Hashimoto et al., 2003), increased glutamate content was found in the SNr, a major output site of the basal ganglia, during HFS of the STN in normal rats (Windels et al., 2000, 2003). Baseline levels of glutamate and GABA were significantly higher in DA depleted rats than that in intact animals. STN DBS significantly increased GABA levels, but not glutamate levels, in the SNr. Interestingly, ibotenic acid lesions of the GP blocked DBS-induced increases in GABA content, suggesting that activation of pallidonigral pathways may partially account for the therapeutic effects of DBS (Windels et al., 2005). The possibility that GABAergic transmission may play a significant role in mediating the effects of DBS is further supported by electrophysiological findings indicating that modulation of GABAergic inputs, but not glutamatergic inputs, is the primary factor regulating the active state of SNr neurons in freely moving rats (Windels and Kiyatkin, 2004).

3.5. Behavioral context-dependent neural responses

Motor processing within the basal ganglia thalamocortical system is a dynamic process by which voluntary movements are generated in response to continuously changing environmental conditions (Grillner et al., 2005). Extensive evidence indicates that basal ganglia thalamocortical circuitry is differentially involved in self-initiated vs. externally triggered motor actions. Behavioral context-dependent neural activity has been observed in both cortical and basal ganglia regions, which may represent distinct pathways for processing specific motor signals in response to interactions with complex environmental conditions.

Single unit recording and functional imaging studies in humans and monkeys have demonstrated that the supplementary motor area (SMA) is activated during self-initiated movement and that the premotor cortex was more likely to be involved in externally triggered movement (Mushiake et al., 1991; Okano and Tanji, 1987; Romo and Schulz, 1987; Taniwaki et al., 2003). Behavioral context-dependent neural activity was also found in the basal ganglia and in thalamic regions (Menon et al., 1998; Cunnington et al., 2002). An fMRI study in healthy humans showed that both the basal ganglia and the SMA were preferentially involved in self-initiated movement. Single unit recording and inactivation studies in the thalamus in monkeys revealed that separate pathways mediate self-initiated (ventral anterior nucleus) and externally triggered (ventral posteriolateral nucleus) movements (van Donkelaar et al., 1999, 2000). Taniwaki and colleagues (2003) examined the activity in several basal ganglia thalamocortical regions during self-initiated and externally triggered finger movements in healthy humans. Their network analysis demonstrated that a strong interaction within the basal ganglia thalamocortical loop was present only during the self-initiated movements. Interestingly, this segregation of motor processing between self-initiated and externally triggered movements was disrupted in PD patients. The finding that the SMA was substantially inhibited in patients with PD suggests that self-initiated movement is primarily affected by PD (Sabatini et al., 2000). Meanwhile, external cues were able to improve motor performance in Parkinsonian patients, suggesting that interaction between these two pathways may exist.

It would be of great interest to establish whether DBS regulates basal ganglia thalamocortical circuitry in a constant manner or whether it involves a dynamic process that is dependent upon the ongoing behavioral context. To address this question, we compared basal ganglia neural responses to behaviorally effective STN DBS between unilateral 6-OHDA lesioned rats performing the treadmill locomotion task and those performing the limb use asymmetry task (Shi et al., 2005). Treadmill locomotion

is considered to be an externally triggered, partially forced movement and performance in the limb use asymmetry test involves self-initiated exploratory movement triggered by internal motivational drive. As discussed above, while HFS of the STN significantly improved both motor tasks in parkinsonian rats (Chang et al., 2003; Shi et al., 2004), SNr neural responses to STN DBS differed between the tasks. In the treadmill locomotion task, inhibitory and excitatory neural responses were approximately equal, whereas in the limb-use asymmetry test, predominantly inhibitory responses were observed in the SNr. This dissociation may be related to the basal ganglia output signals coding different behavioral contexts, rather than differential effects of DBS within the STN as the local neural responses in the STN were similar between these two behavioral tasks.

The dissimilar behaviors involved in these tasks (treadmill walking vs. rearing) make it difficult to discern whether the different neural responses are due to the different behavioral contexts or the different motor performances. To solve this problem, we developed a wheel running task in which rats were trained to run in the wheel either voluntarily or by force. For voluntary running, rats were placed in the running wheel without any manipulation, and the running bouts, total running distance and running speed were recorded during a 1 h experimental session. For forced running, a computer controlled motor was turned on and off at twenty second intervals. Unilateral 6-OHDA lesion-induced changes were apparent in both the voluntary and the forced versions of the wheel running test. In the voluntary running task, both the distance of total running and number of running bouts per session were significantly reduced following the lesion. In the forced running task, the lesioned rats exhibited signs of akinesia that were similar to that observed in the treadmill locomotion test. Lesioned rats could not follow the wheel as well as neurologically intact rats. Instead of actively running in the bottom center of the wheel, lesioned rats were often carried to the up slope of the wheel and struggled to catch up with the turning wheel. STN DBS restored normal locomotion in voluntary running tests. DBS also restored normal running patterns in the forced running test and the lesioned rats were able to run in the proper bottom center position of the running wheel. The lesion-induced motor deficit during wheel running is likely caused by DA depletion, as the degree of DA depletion correlated closely with running distance in the spontaneous wheel running experiment.

Preliminary electrophysiological studies have revealed dissociation in DBS induced neural responses in the motor cortex between spontaneous and forced wheel running (unpublished observations). Interestingly, predominantly excitatory neural responses were observed in the voluntary wheel running experiments, whereas inhibitory responses outnumbered excitatory responses in the forced running experiments. These results echo the findings of the imaging study in patients with PD, in that decreased activity was found in an area that is involved in self-initiated movements, and increased activity was found in an area that is involved in externally triggered activity (Sabatini et al., 2000). Excitatory responses to DBS observed in spontaneous wheel running counteracted the decreased activity during self-initiated movement observed in Parkinsonian patients, and inhibitory responses to DBS during forced wheel running counteracted the increased activity during externally triggered movement observed in Parkinsonian patients. These preliminary results suggest that DBS may counteract the abnormal cortical activity underlying the bradykinesia suffered by PD patients across different behavioral contexts.

4. Concluding remarks and future directions

Rodent models have been used successfully in PD research for over three decades and continue to contribute to emerging research fields, such as DBS. Several behavioral models have been developed to study the effects of DBS in Parkinsonian rats. Similar to the effects of DBS in human patients, HFS of the rat STN can alleviate motor deficits in a variety of motor tasks. Rat, being quadripedal and human being bipedal, superficially seems to exhibit different motor patterns, but the basic essence of the deficits is clearly similar. These models, when applied properly, can be used to study several issues related to the mechanisms of DBS, such as motor processing, sensorimotor integration, motivation and cognitive functions. Numerous electrophysiological studies have been carried out to characterize HFS-induced neural activity changes. Due to differences in preparations (*in vitro* vs. *in vivo*), experimental conditions (anesthetized vs. behavioral) and stimulation parameters, the results have varied greatly among different laboratories. While *in vitro* studies enable the molecular events and alterations in membrane properties during DBS to be examined precisely, *in vivo* studies reveal basal ganglia neural responses with intact neural circuitry. Furthermore, single unit recording during behaviorally effective DBS in freely moving, Parkinsonian rats provides a direct revelation of the changes in neural processing that may underlie the therapeutic effects of DBS. Single unit recording methods, in combination with imaging and local field potential measurements within structures, will advance our knowledge of how DBS alleviates Parkinsonian symptoms. Issues of how DBS may affect other behavioral modalities, including sensorimotor integration and cognitive functions, merit further exploration. Technological improvements, such as noise suppression and real time computation, will facilitate the development of closed-loop, brain computer interface methods that can deliver optimal DBS that is more therapeutically effective and energy efficient.

Acknowledgments

Several of the studies presented in this article were supported by NIH Grants NS-43441, NS-40628 and TW-006144 to J.Y.C. and NS-19608 to D.J.W.

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