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Review

Pathophysiology of the basal ganglia and movement disorders: From animal models to human clinical applications

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Abstract

Electrophysiological studies in control and MPTP treated primates have played a major role in our understanding of the physiology of the basal ganglia and the pathophysiology of Parkinson's disease (PD). Early models emphasized discharge rate and viewed the basal ganglia as a network of boxes (nuclei) connected by excitatory or inhibitory connections. More recent studies view the basal ganglia as neural networks with weak and non-linear interactions in and between the different nuclei.

Microelectrode electrophysiological recording enables the high resolution—both in the temporal domain (spike) and the spatial domain (neuron)—required for the *in vivo* investigation of neuronal networks of the basal ganglia. MPTP treated primates exhibit the full pathological and clinical spectrum of human Parkinsonism and therefore their electrophysiological study has promoted better understanding of the normal state, the dopamine-depleted state, and finally the testing of potential therapeutic interventions for PD. Here, we review the main insights learned from microelectrode physiological studies of MPTP monkeys over the last 20 years since the introduction of this animal model.

Keywords: Parkinson's disease; MPTP; Primate; Neural network; DBS

Contents

1. The MPTP primate model of Parkinsonism

MPTP was introduced to the Parkinson's disease (PD) research community when it was found to have contaminated batches of a synthetic heroin analog that was self-administered by drug addicts. These individuals developed an acute syndrome with all the cardinal symptoms of PD including bradykinesia, akinesia, muscle rigidity and some degree of resting tremor (Langston et al., 1983; Ballard et al., 1985). This unfortunate human incident led to the introduction of a new primate model for PD (Burns et al., 1983; Langston et al., 1984). Monkeys treated with MPTP exhibit most of the akinetic-rigid cardinal symptoms of PD

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(Burns et al., 1983; Doudet et al., 1985; Schultz et al., 1985, 1989a, b). Low frequency (4–8 Hz) resting tremor is not readily replicated in MPTP treated macaque monkeys (Jenner et al., 1986; Miller and DeLong, 1987; Benazzouz et al., 1992; Wilms et al., 1999), but some species, notably the African green (vervet) monkey can develop a prominent low-frequency (4–7 Hz) postural/action tremor (Redmond et al., 1985; Bergman et al., 1994; Raz et al., 2000).

From post-mortem examination of the brains of MPTP-treated monkeys it appears that the primary insult is to the dopaminergic system. Tyrosine hydroxylase (TH) immunoreactivity reveals loss of TH-positive staining in the terminal fields of the dopamine (DA) neurons in the striatum as well as in their cell bodies in the substantia nigra (Elsworth et al., 2000; Song and Haber, 2000; Bezard et al., 2001). However, as in human PD other neuromodulators are also affected (Pifl et al., 1991).

The extent of neuronal damage and the severity of the resulting Parkinsonian symptoms strongly depend on the protocol used to administer the MPTP. The most common protocol is the systemic injection of MPTP. Depending on the total dosage, the number and the frequency of injections used, monkeys can develop a full spectrum of responses ranging from severe Parkinsonism (Chiueh et al., 1985) to a mild clinical state dominated by frontal cognitive deficits but lacking motor signs (Schneider and Kovelowski, 1990; Schneider, 1990; Roeltgen and Schneider, 1994; Schneider and Pope Coleman, 1995; Slovin et al., 1999). In contrast to the human pathology (Kish et al., 1988), acute MPTP treatment produced DA depletion that is equal or more severe in the caudate nucleus than in the putamen (Pifl et al., 1988).

Chronic low-dose MPTP exposure has been suggested as a more reliable model of the slowly progressing human disease (Schneider, 1990; Hantraye et al., 1993; Perez Otano et al., 1994). In animals, chronically treated with low doses of MPTP there is a greater decrease of DA in the dorsolateral (putaminal) portions of the striatum. Frontal cognitive deficits, and abnormal eye movements can be observed in these animals even before the development of motor deficits (Schneider and Kovelowski, 1990; Schneider and Roeltgen, 1993; Slovin et al., 1999). This is in line with early cognitive deficits found in human MPTP (Stern and Langston, 1985; Stern et al., 1990) and PD patients (Brown and Marsden, 1990).

Other MPTP experimental methods include administration of MPTP by intracarotid injection (Bankiewicz et al., 1986; Eberling et al., 1998) or by striatal mini-pumps (Matsumoto et al., 1999). These methods are very useful since they produce hemi-Parkinsonism, enabling easier control of the animals' health and feeding. However, because of their unilateral effects, the confounding compensatory interaction between the two hemispheres and the bilateral (although not symmetric) nature of the human disease they are usually consider inferior to the systemic MPTP models.

2. Discharge rates in the basal ganglia and the "box and arrow" rate model

The severe motor disorders associated with basal ganglia malfunction following striatal dopamine depletion have been traditionally attributed to the change of overall activation of these nuclei and changes in the net effect they exert on the cortex (Albin et al., 1989; DeLong, 1990).

Several primate studies have shown that MPTP has a differential effect on firing rates in the internal and external segments of the globus pallidus (GPi and GPe, respectively). The tonic firing rate of GPi neurons increases from ~80 to ~100 spikes/s (Miller and DeLong, 1987; Filion and Tremblay, 1991; Boraud et al., 1996, 1998c, 2000, 2001), while the rate of GPe neurons decreases from ~70 to ~50 spikes/s (Miller and DeLong, 1987; Filion and Tremblay, 1991; Boraud et al., 1998b, 2000; Raz et al., 2000). The tonic firing rate of subthalamic nucleus (STN) neurons increases after MPTP from ~20 to ~25 spikes/s (Bergman et al., 1994). Although all these rate changes reflect alterations of 20–50% of average firing rate, it is important to be aware of the large variability of firing rate, both in the normal and in the MPTP state, yielding almost overlapping distributions of discharge rates in these structures before and after MPTP.

The changes in the spontaneous firing rates of striatal neurons following DA depletion are less clear than the above-mentioned changes in the pallidum and the STN. In the striatum, one must differentiate between phasically active neurons (PANs) and the tonically active neurons (TANs) (Wilson, 1993; Aosaki et al., 1995). The PANs are the medium spiny GABAergic projection neurons of the striatum. Studies of primate PANs are lacking, and there is no consensus regarding the effect of dopamine depletion on this population of striatal neurons in rodent and cat studies (Yoshida, 1991; Rothblat and Schneider, 1993; Kiyatkin and Rebec, 1996; Tseng et al., 2001). The TANs are probably the cholinergic interneurons of the striatum, and constitute ~1–2% of striatal neurons (Aosaki et al., 1995; Kawaguchi et al., 1995; Wilson, 2003). The basal firing rate of the TANs is not affected by MPTP treatment (Aosaki et al., 1994; Raz et al., 1996); however, their firing patterns and synchronization are modified.

The changes in pallidal discharge rate are best understood in the framework of the "box-and-arrow" rate model of the basal ganglia circuitry (Albin et al., 1989; DeLong, 1990). Here, we start with a brief description of this "textbook" model and its successful predictions; however, we have included a section describing the shortcomings of the model. This "box and arrow" model depicts the general feed-forward loop structure of the basal ganglia network. The model's main claim is that there exist two segregated striatal pathways that converge on the GPi. The "direct pathway" is a di-synaptic inhibitory pathway from the cortex to the GPi via the striatum. The "indirect pathway" is a polysynaptic *disinhibitory* pathway from the cortex to GPi via the striatum and the GPe and the STN. Early

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histochemical and pharmacological studies suggested that the direct and indirect striato-pallidal pathways are based on two segregated populations of striatal GABAergic projection neurons. The projection striatal neurons in the direct pathway contain substance P and dynorphin and express D_1 dopamine (DA) receptors, whereas those in the indirect pathway contain enkephalin and express D_2 DA receptors (Gerfen et al., 1990; Aubert et al., 2000). Midbrain DA has differential effects on the two striato-pallidal pathways: it facilitates transmission along the direct pathway via the D_1 receptors and inhibits transmission along the indirect pathway via the D_2 receptors (Albin et al., 1989; Gerfen et al., 1990; DeLong, 1990; Wichmann and DeLong, 1996).

Indeed, the MPTP-induced changes in the average firing rates of the STN and both pallidal segments described above are in line with the predictions of this "box and arrow" model. The decrease in DA levels (due to the MPTP insult) leads to an effective weakening of the direct pathway (less excitatory D_1 modulation of striato-pallidal neurons) and to a strengthening of the indirect pathway (less inhibitory D_2 modulation of striato-pallidal neurons). As a result, the GPi is overexcited due to the increased STN activity and is disinhibited via the direct striato-pallidal pathway resulting in an increase of its basal discharge rate. This effective excitation of GPi leads to excessive inhibition of frontal cortex, which in turn leads to Parkinsonian akinesia. The tremor phenomenon has been explained as being due to tonic hyper-polarization of thalamic neurons, switching them from burst-mode to an oscillatory firing pattern (Llinas, 1988; Pare et al., 1990).

3. Inactivation and high frequency stimulation of deep brain structures of PD patients

The box and arrow model of the basal ganglia and the findings of increased firing rates in the STN and GPi predicted that ablation or inactivation of GPi or STN would lead to the alleviation of Parkinsonian symptoms. Indeed, STN lesions and inactivation (by injection of the GABA agonist muscimol) have been shown by several groups to reverse Parkinsonian symptoms in MPTP primates (Bergman et al., 1990; Aziz et al., 1991; Guridi et al., 1993; Wichmann et al., 1994; Guridi et al., 1996). Injection of excitatory amino acid antagonists into the GPi of MPTP-treated monkeys reverses the motor symptoms of Parkinsonism (Graham et al., 1990). These primate observations correlated well with previous neurosurgical treatments of PD (Laitinen et al., 1992). Pallidotomy which had been largely abandoned since the advent of levodopa therapy, was "revisited" and shown to be very successful at alleviating PD symptoms in human patients (Laitinen et al., 1992; Lozano et al., 1995; Vitek and Bakay, 1997). Moreover, the primate results set the stage for the introduction of the STN as a neurosurgical target for the treatment of PD patients (Benabid et al., 1994; Obeso et al., 1997; Gill and Heywood, 1997; Krack et al., 2003).

High frequency electrical stimulation of the target nuclei had been used to confirm the location of the thalamic VIM target ever since the early days of ablative stereotactic surgery for tremor. Empiric clinical observation during those procedures revealed that high frequency stimulation (HFS) would reduce or abolish tremor in these patients. This prompted the assumption that electrical stimulation, and especially HFS, had the same effect as ablation; namely inhibition of neuronal discharge in the target nucleus. More importantly, this observation encouraged the use of chronically implanted macrostimulating electrodes for treating movement disorders, leading to the replacement of ablation by deep brain stimulation (DBS) therapy as the preferred technique for human patients (Benabid et al., 1994; Limousin-Dowsey et al., 1999). DBS of the STN or of the GPi has been very successful at alleviating Parkinsonism both in PD patients (Limousin et al., 1995; Pollak et al., 1996; Kumar et al., 1998) and in MPTP primates (Benazzouz et al., 1996). Today DBS is preferred to ablative surgery due to its reversibility, the option of bilateral therapy and parameter tuning capabilities (Lang and Lozano, 1998; Gross et al., 1999) enabling adjustment of the DBS effects to the evolution of the dopamine damage and the clinical symptoms of the patient.

4. The shortcomings of the box-and-arrow model of the basal ganglia

Although the most critical prediction of the "box-and-arrow" rate model, i.e., alleviation of PD symptoms by inactivation of the GPi or the STN is indeed observed, the accumulation of new anatomical, physiological and clinical data casts doubt on the validity of the model. According to the box-and-arrow rate model, inactivation of the GPi should alleviate akinesia, bradykinesia and rigidity. However, pallidotomy has been shown to be primarily effective in alleviating l-dopa induced dykinesias (Lozano et al., 1995; Baron et al., 1996; Lang et al., 1997). This actually contradicts the logic of the model: removal of pallidal inhibition should, if anything, exacerbate dyskinesias (Marsden and Obeso, 1994). A critical assumption of the box-and-arrow model is the segregation of the D_1-direct striato-pallidal pathway from the D_2-indirect-striato-pallidal pathway. However, there is evidence that both D_1 and D_2 DA receptor subtypes are often co-localized on the *same* striatal neurons (Surmeier et al., 1993, 1996; Nicola et al., 2000; Aizman et al., 2000). The box-and-arrow rate model infers differential effects of dopamine on the direct and the indirect (D_1-induced excitation of the direct striato-GPi pathway vs. D_2-induced inhibition of striatal neurons projecting to the GPe). Although application of DA to striatum produce mixed responses among striatal neurons (Johnson et al., 1983; Toan and Schultz, 1985), the differential D1/D2 response prediction has not been verified by direct electrophysiological studies. Furthermore, striatal neurons projecting to GPi have been shown

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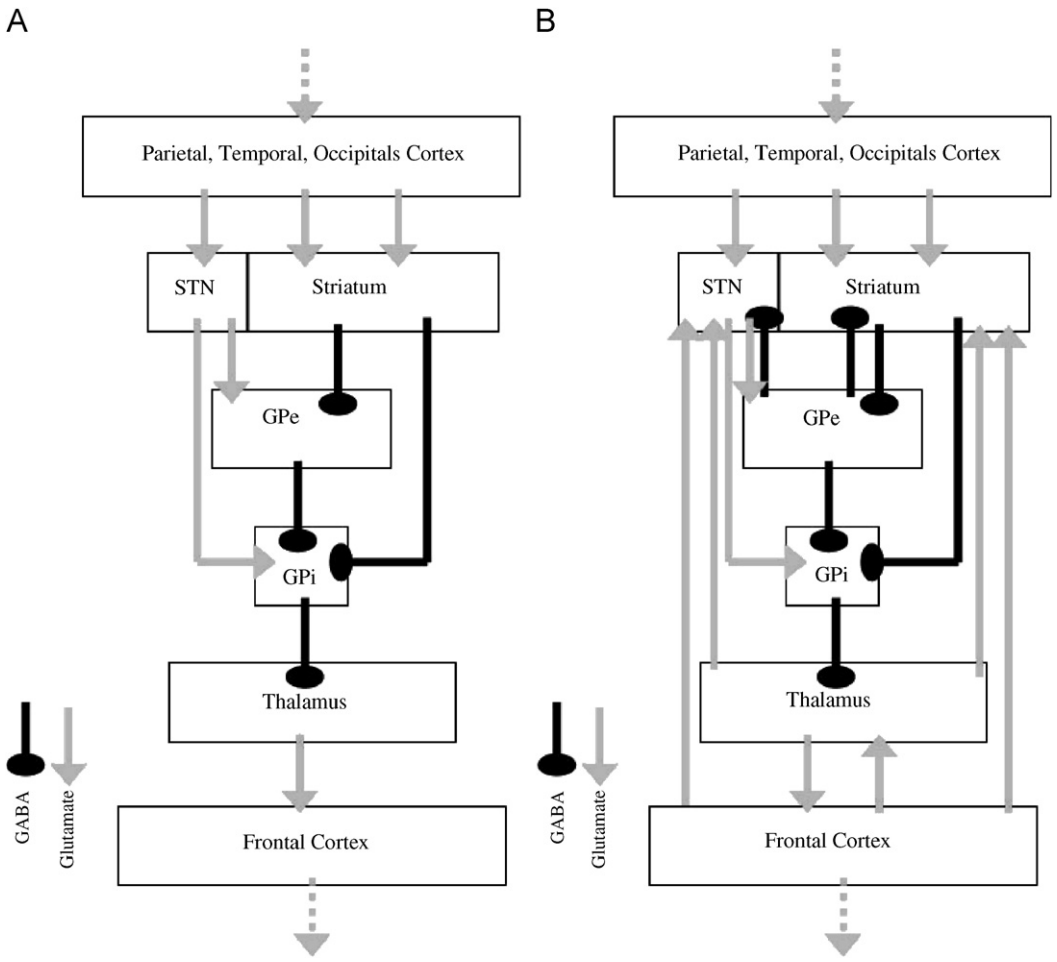

Fig. 1. Current view of the inter-nuclei connectivity of the cortex-basal ganglia networks. (A) Schematic view and (B) detailed representation of the basal ganglia connectivity; STN: subthalamic nucleus, GPe, GPi: external, internal segment of the globus pallidus.

to send collaterals to GPe in rodents (Kawaguchi et al., 1990), as well as in primates (Parent and Hazrati, 1993; Parent et al., 2000; Levesque and Parent, 2005).

The evolving picture of the basal ganglia connectivity is much more complex than the simplified view of the direct and the indirect pathway. The direct projections from the motor cortex to the STN (the "hyper-direct" pathway"; Nambu, 2004) suggest that, like the striatum, the STN is an input stage of the basal ganglia. Moreover, the feedback projections from the GPe to the striatum (Bolam et al., 2000), as well as the GPe to GPi projection (Hazrati et al., 1990), depicts the GPe as a central nucleus in the basal ganglia circuitry, rather than a simple relay station in the indirect pathway. Fig. 1 summarizes the current view of the complex connectivity between the basal ganglia nuclei.

In line with the new anatomical evidence of a highly complex basal ganglia network, several recent electrophysiological primate studies have failed to find consistent changes in GPe firing rates (Bezard et al., 1999; Raz et al., 2000; Boraud et al., 2001), or in GPi firing rates in all MPTP monkeys (Bergman et al., 1994; Wichmann et al., 1999; Raz et al., 2000). Similarly, biochemical and metabolic studies indicate that GPe activity does not change in Parkinsonism (Levy et al., 1997). The "box and arrow" model predicts that the enhanced GPi inhibitory output in Parkinsonism should reduce motor cortex firing rates, resulting in akinesia, bradykinesia and rigidity. However, several studies in DA depleted primates have not shown any change in spontaneous thalamic (Pessiglione et al., 2005) or motor cortical firing rates (Gross et al., 1983; Doudet et al., 1990; Watts and Mandir, 1992; Goldberg et al., 2002).

Finally, the box-and-arrow rate model is a static model that attempts to explain akinesia in terms of changes in tonic firing rates. However, the model fails to account for the dynamic symptoms of PD, rigidity and resting tremor. PD resting tremor is presumably related to changes in neuronal firing *patterns* and to the onset of *oscillatory* discharge in the cortico-basal ganglia circuitry.

5. Discharge pattern, synchronization and neural-network models of basal ganglia circuitry

The accumulation of experimental evidence against the box-and-arrow rate model of the basal ganglia has been paralleled by recognition of the *conceptual* disadvantages

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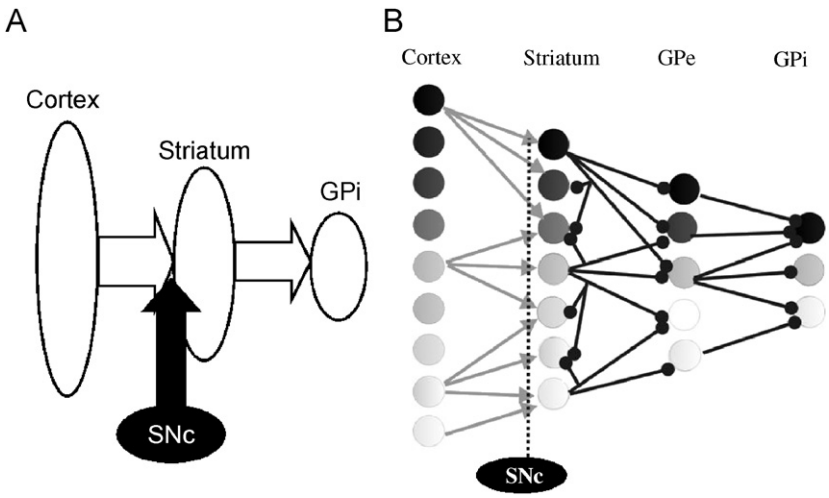

Fig. 2. The reinforcement-driven dimensionality reduction model of the basal ganglia. (A) A schematic representation of the main axis of the basal ganglia. (B) Neural network model representation showing the convergence/divergence neuronal connections in the basal ganglia. Gray arrows represent glutamatergic-excitatory connections, and black arrows represent—GABAeregic inhibitory connections. Dopamine projections from the substantia nigra pars compacta (SNc) affecting the efficacy of the cortico-striatal synapses are depicted as broken line. GPe, GPi: external, internal segment of the globus pallidus.

of this model. The model treats each basal ganglia structure as a single monolithic entity and ignores the large number of cells in each structure, the diversity of cell types and the elaborate microcircuitry within each structure. Furthermore, the model does not explain the role of basal ganglia during the execution of normal movements. This set the stage for the development of new models of basal ganglia function (Beiser et al., 1997; Gillies and Arbuthnott, 2000; Gurney et al., 2004).

Anatomical studies have suggested that afferents from the STN excite a large number of neurons within the GP, while the striatum exerts a more focused inhibition on a subset of these neurons (Parent and Hazrati, 1993; but see Smith et al., 1998). Mink (1996) expanded on this observation and proposed a more general principle of basal ganglia function, namely the *action–selection* scheme. According to this model, the function of the basal ganglia is to select a desired motor plan (by disinhibiting the thalamo-cortical circuits involved in this plan) while inhibiting competing ones. This is achieved by way of both a center-surround configuration of the focused striatal inhibition (Mink, 1996) and also by the temporal differences between striatal and STN input to GPi (Nambu, 2004). It was then hypothesized that in Parkinsonism the action–selection mechanism fails due to inadequate over inhibition of all possible actions.

The simplified version of the action–selection model may be challenged by two physiological observations. First, changes in pallidal activity lag behind movement initiation (DeLong, 1971; Anderson and Horak, 1985; Turner and Anderson, 1997). Second, the action–selection model predicts a positive correlation between the discharge of pallidal neurons participating in the same action, and a negative correlation between pallidal neurons that participate in competing actions. However, physiological studies fail to reveal such relationships between simultaneously recorded basal ganglia neurons (Jaeger et al., 1994; Nini et al., 1995; Raz et al., 2000; Bar-Gad et al., 2003a).

A model that combines most of the anatomical and physiological approaches cited above was recently proposed (Bar-Gad and Bergman, 2001; Bar-Gad et al., 2003b). The model assumes that the basal ganglia performs efficient dimensionality reduction, or efficient extraction (Diamantaras and Kung, 1996; Seung and Lee, 2001) and de-correlation of the large information space spanned by the activity of the cortico-striatal neurons. Dimensionality reduction is a mapping of a multidimensional space into a space of fewer dimensions. This means that the original feature space is transformed by applying a linear transformation (e.g., via a principal components analysis) or non-linear transformation into a smaller and more compact space. Consider a string of beads, first 100 black and then 100 white. If the string is wadded up, a classification boundary between black and white beads will be very complicated in three dimensions. However, there is a (non-linear) mapping from three dimensions to one dimension, namely distance along the string, which makes the classification trivial. Theoretical studies demonstrate that neural networks can perform such efficient coding using locally competitive synaptic learning rules (Diamantaras and Kung, 1996). Fig. 2 summarizes the neural network representation of the main axis of the basal ganglia.

A critical feature of this network model is the assumption that the dimensionality reduction along the basal ganglia axis is affected not only by the properties of the cortical patterns but also by their behavioral significance. This is achieved by the triple striatal synapse in which the DAergic signals control the feed-forward cortico-striatal connections. The DAergic signals are proportional to the degree of mismatch between the subject's predictions and

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reality (Schultz, 1998; Fiorillo et al., 2003; Morris et al., 2004). The reinforcement signal causes the extraction of the cortical information to become discriminative, resulting in better compression of cortical information about reward-related inputs but not about unrelated events. Finally, DA depletion as occurs in PD can impair the dimensionality reduction process. The consequential modifications of the basal ganglia synapses are predicted to result in increased synchronization among pallidal neurons (Nini et al., 1995; Hurtado et al., 1999; Levy et al., 2000; Raz et al., 2001).

Action–selection is an extreme form of dimensionality reduction (e.g., from the high dimensional cortical information to one or a few actions). The main difference between the action selection and the dimensionality reduction models is that in the latter model the basal ganglia are not restricted to selection of a few actions. Rather, the basal ganglia are part of a circuit that uses optimal and reinforcement-driven data compression tools in order to develop the appropriate multi-dimensional activity that is projected to the frontal cortex. The dimensionality reduction model is consistent with the recent findings of strong modulation of basal ganglia activity by reinforcement and learning (Graybiel et al., 1994; Kawagoe et al., 1998; Jog et al., 1999; Schultz et al., 2003; Samejima et al., 2005) and may therefore represent a better model (at least in our view) for basal ganglia physiology and pathophysiology.

As predicted by the dimensionality reduction closed model of the basal ganglia, firing patterns in many areas of the nervous system of primates are dramatically altered following MPTP-treatment. There is an increase in the percentage of neurons that discharge in bursts. These bursts are either irregular or oscillatory and have been found in STN, GPe, GPi and also in primary motor cortex (Miller and DeLong, 1987; Filion and Tremblay, 1991; Bergman et al., 1994; Nini et al., 1995; Boraud et al., 1998a; Wichmann et al., 1999; Raz et al., 2000; Goldberg et al., 2002). Moreover, physiological studies of the pallidum in MPTP-treated monkeys demonstrate that their pair-wise crosscorrelograms become peaked and oscillatory, suggesting that DA depletion induces an abnormal coupling of basal ganglia loops. Similar findings of increased synchronization within primate brains following MPTP-treatment have been found in primary motor cortex (Goldberg et al., 2002), among striatal TANs and between TANs and pallidal neurons (Raz et al., 1996, 2001). Finally, dopamine replacement therapy normalize the neuronal synchronization among pallidal neurons (Heimer et al., 2002).

6. DBS mechanisms

Although DBS has revolutionized the neurosurgical treatment of PD, the basic mechanisms of DBS are still not clear (Benabid, 2003; Lozano and Eltahawy, 2004; Garcia et al., 2005). Ranck (1975) and Asanuma and co-workers (Stoney et al., 1968) showed that when metal microelectrodes (exposed tip $\cong$5–15 μm; impedance $\cong$0.5–10 MΩ at 1000 Hz) are used for stimulation, the susceptibility of nerve fibers to the stimulation is much higher than that of the cell bodies, suggesting that microstimulation activates bypassing fibers. The classical interpretation of the effect of micro-stimulation on the motor cortices has been that the stimulation induces excitation of the cortex or cortico-spinal axonal pathways and thus evokes movement of different body parts. The microexcitabilty of the primate striatum (Alexander and DeLong, 1985a, b) has been similarly explained. Nevertheless, the effect of DBS in PD is paradoxically similar to the effect of lesions (e.g., neuronal *in*activation) and therefore the question of the actual effect of DBS is still under intensive study. There are several possible mechanisms to explain DBS results: depolarization block of the "stimulated" neurons, stimulation of bypassing inhibitory pathways, and/or induction of GABA release from the terminals of the GPe projection neurons, thereby inhibiting the target GPi neurons.

Application of DBS to the STN of MPTP primates has generated conflicting results. In early studies, DBS was found to differentially affect the mean discharge rates in the GPe and GPi for several hours after the DBS: it caused an increase in the GPe and a decrease in the GPi (Hayase et al., 1996; Boraud et al., 1996; Benazzouz et al., 2000; Dostrovsky et al., 2000). However, in a recent study the mean firing rates increased in *both* pallidal segments during DBS (Hashimoto et al., 2003). DBS with STN macro-electrodes has been recently shown in rats *in vitro* to directly activate the membrane potential of the STN neurons (Garcia et al., 2003). Indeed, more recent studies indicate complex locking of GP activity to the high-frequency stimulation applied to the GP (Bar-Gad et al., 2004; Hashimoto et al., 2003; Garcia et al., 2003). These results suggest that DBS effects are not primarily mediated by inhibition of the targets. Our current working hypothesis is that DBS enforces a constant spatio-temporal discharge pattern in the output structures of the basal ganglia. Although it is possible that this constant spatio-temporal firing pattern imposes a new basal ganglia output message, it is attractive to consider it as a null message (the "jamming" hypothesis; Benabid, 2003). Such a null discharge pattern from the basal ganglia is ignored by the thalamo-cortical circuits, and enables compensation by the rich recurrent cortical networks. The recent findings of the beneficial effects of motor cortex stimulation (Drouot et al., 2004; Lefaucheur et al., 2004), both in the MPTP primate and in human PD patients, further highlight the complex effects of deep and cortical high-frequency stimulation, and suggest that the major effects of DBS are due to modification of the abnormal output of the Parkinsonian basal ganglia-cortical networks and the facilitation of cortico-cortical compensatory processes.

7. Summary and prospective work in the MPTP primate model of Parkinsonism

The MPTP primate model is unquestionably currently the best experimental model for PD. It enables researchers

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to study the pathology of a form of Parkinsonism that is very similar to idiopathic human PD. Electro-physiological studies in this model have enabled us to probe the ongoing activity of neurons in the basal ganglia networks of normal, Parkinsonian and DA agonist-treated primates. These studies paved the way to the hypothesis that inactivation of the primate STN would lead to alleviation of Parkinsonism and prompted inactivation and DBS of the STN as the major neurosurgical treatment of advanced PD. More recently, it was found that Parkinsonism is accompanied by a breakdown of the spatio-temporal function of the basal ganglia networks manifested by the onset of synchronized neuronal bursts and high frequency oscillations. These findings may call for development of future therapies that will target this abnormal synchronization (Tass, 1999).

However, many questions remain to be answered. Recently, new potential drug therapies have been offered for PD, e.g., specific glutamate antagonists or adenosine A2A antagonists (Mori and Shindou, 2003; Kase et al., 2003). Similarly, "new" anatomical targets, e.g., the motor cortex (Drouot et al., 2004) and the pedunculopontine nucleus (Pahapill and Lozano, 2000; Jenkinson et al., 2005), have been suggested as loci for high-frequency stimulation therapies of Parkinson's disease. Our central model based on glutamate and GABA as carriers of information along the basal ganglia networks and dopamine as the modulator of the efficacy of the cortico-striatal transmission should be fine-tuned to cope with this new neurochemical, anatomical and clinical information. Future studies of the neural networks of the basal ganglia, in health and disease, should enable us to further shed light on these structures, and by doing so to provide better therapies for their disorders.

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