What do the Basal Ganglia Do?

- A modeling Perspective

V. S. Chakravarthy[1], Denny Joseph[1], Raju S. Bapi[2],

[1]*Department of Biotechnology,*

Indian Institute of Technology, Madras, Chennai 600036.

[2]*Department of Computer and Information Sciences and*

Center for Cognitive Sciences,

Unviersity of Hyderabad, Hyderabad 500046.

Abstract

Basal ganglia (BG) constitute a network of 7 deep brain nuclei involved in a variety of crucial brain functions including: action selection, action gating, reward based learning, motor preparation, timing etc. In spite of the immense amount of data available today, researchers continue to wonder how such a small deep brain circuit performs such a bewildering range of functions. Computational models of BG have focused on individual functions and fail to give an integrative picture of BG function. A major breakthrough in our understanding of BG function is perhaps the insight that activities of mesencephalic dopaminergic cells represent some form of 'reward' to the organism. This insight enabled application of tools from 'reinforcement learning,' a branch of machine learning, in the study of BG function. Nevertheless, in spite of these bright spots, we are far from the goal of arriving at a comprehensive understanding of these 'mysterious nuclei.' A comprehensive knowledge of BG function has the potential to radically alter treatment and management of a variety of BG-related neurological disorders (Parkinson's disease,

Huntington's chorea etc.) and neuropsychiatric disorders (Schizophrenia, Obsessive Compulsive Disorder etc.) also. In this article, we review the existing modeling literature on BG and hypothesize an integrative picture of the function of these nuclei.

Keywords: Basal ganglia, dopamine, reinforcement learning, actor critic models, action selection, exploration.

Outline

1.0 Introduction

Basal Ganglia (BG) are deep brain nuclei implicated in diverse and crucial functions like 1) reward based learning, 2) exploratory behavior, 3) goal-oriented behavior, 4) motor preparation, 5) working memory, 6) timing, 7) action gating, 8) action selection, 9) fatigue and 10) apathy. In his Robert Wartenberg lecture on BG, eminent neurologist C. Marsden described these nuclei as being 'mysterious' (Marsden 1982). Although much work has been done since Marsden's lecture, our knowledge of BG is fraught with controversies, a deficiency which surfaces in the form of uncertainties involved in therapeutics of various BG-related disorders like Parkinson's disease, for example. The question that continues to puzzle researchers is: how are such an overwhelming range of functions supported by such a small subcortical circuit?

A key idea that opens doors to understanding of BG function is the idea that activity of dopaminergic cells in BG represents *reward signaling* (Schultz 1998). This conceptual association enabled application of 'reinforcement learning' (RL) concepts (Sutton & Barto 1998) to BG research. RL is a branch of machine learning which studies how an agent learns to respond to stimuli optimally without an explicit teacher; the agent's learning process is driven by the reward/punishment signals that come from the environment in response to the agent's actions. RL today enjoys excellent applications in robotics (Dorigo and Colombetti, 1996, Yong et al, 2007). Computational RL is in fact inspired by instrumental conditioning, a topic from psychology, in which an animal learns to produce rewarding responses to sensory stimuli (Sutton & Barto 1990). Responses that result in rewards are reinforced and those that lead to punishment are avoided. This search for rewarding responses typically involves a trial and error or an

exploratory process. Therefore, if BG is assumed to subserve reinforcement learning dynamics, their role in *exploratory behavior* is easily anticipated. Reward is an abstract notion and must be carefully defined before we present a perspective on BG function. While food or juice rewards are primary forms of reward, a more abstract (secondary) form of reward may be thought to be successful approach to and arrival at a goal state. There is considerable experimental literature that points to involvement of BG in *goal-oriented behavior*. *Motor preparation* is often defined, rather vaguely, as what the brain does *before* movement execution begins. Although BG has been thought to be involved in motor preparation, there was no convincing theory of BG's role in motor preparation. We describe motor preparation as being accomplished by interaction between BG and motor cortex. Goal-oriented behavior requires that the goal state be sustained in the form of appropriate *working memory* representations. There is increasing recognition of the role of dopaminergic projections in sustaining and updating working memory representations in prefrontal cortex. An important component of RL is prediction of future rewards. Predicting potential rewards associated with a stimulus-action pair consists of not only predicting the presence/absence or even magnitude of rewards, but also the time of occurrence of reward in the future. Thus the machinery that subserves RL mechanisms is naturally suited to learn *timing* of rewarding future events. Determining the most rewarding response to a given stimulus involves comparison of a multitude of potential actions in a given context, and selecting the best one. BG has been dubbed as the vertebrate brain's answer to the *action selection* problem. Thus, a majority of BG functions can be at least conceptually accommodated within the framework of RL, even though a more detailed and precise knowledge is awaited in several areas. However, there

are aspects of BG function - fatigue, apathy etc. - which do not seem to lend themselves to be captured, in any obvious way, within the net of RL. These offer some of the hardest challenges to modelers in future BG research.

In this article we review a representative portion of the extensive literature on computational models of BG function. Although we strive to present a comprehensive review of literature and a summary of contemporary thinking on this perplexing module in neuroanatomy, our real objective is to collect the many strands of modeling efforts, to unify them under the umbrella of RL, and present a coherent, integrative picture of BG function.

2.0 Basal Ganglia Anatomy:

There have been many excellent summaries of the anatomy of the BG (Gerfen & Wilson, 1996; Mink, 1996; Smith et al, 1998). Fortunately, there is not much controversy about the anatomy of BG though certain questions regarding cellular level connectivity patterns are still being investigated. The more difficult problem is that of BG function and that is the subject matter of this review.

2.1 BG Nuclei:

The BG consist of five nuclei, portions of which play a major role in normal voluntary movement (Gerfen & Wilson 1996). They do not however have direct input or output connections with the spinal cord. These nuclei receive their primary input from the cerebral cortex and send their output to the brain stem and, via the thalamus, back to the

prefrontal, premotor, and motor cortices. The motor functions of the basal ganglia are therefore mediated, in large part, by motor areas of the frontal cortex.

The BG consists of five extensively connected subcortical nuclei: the caudate nucleus, Putamen, Globus Pallidus (interna and externa), Subthalamic nucleus (STN), and Substantia nigra (pars Compacta SNc, and pars reticula SNr). Caudate and Putamen are together constitute the Striatum (STR), which is the input nucleus of the BG. Globus Pallidus can be divided into two parts, viz., Globus Pallidus externa (GPe) and Globus Pallidus interna (GPi). SNc projects axons of dopaminergic neurons onto the STR. The neurons of the STR project to the GPi and to the GPe. Also there exist excitatory and inhibitory connections between the STN and the GPe. The STN neurons project onto the GPi. The nuclei GPi and SNr constitute the output nuclei of the BG, which send GABAergic projections to the thalamus. The cells of the SNc are dopaminergic; dopaminergic cells are also found in the Ventral Tegmental Area (VTA), a medial extension of the pars compacta.

2.2 BG Input/Output:

The BG receive inputs from most of the sensory-motor areas of the cerebral cortex, including primary and secondary somatosensory areas, primary motor cortex (M1) and a variety of premotor areas, including supplementary area, the dorsal and ventral premotor areas. The anatomical basis of motor functions of BG is illustrated in Fig. 2.1. The portions of the cortex that are responsible for movement, namely, the Supplementary Motor Area (SMA), Premotor (PM), Primary Motor Area (M1), somatosensory cortex, and the superior parietal lobule make dense, topographically organized projections to the

motor portion of the Putamen (input nucleus of the BG). The output of this pathway, termed the motor circuit of the BG, is directed primarily back to the SMA and PM cortex. These areas are reciprocally interconnected with each other and with motor cortex and all three have direct descending projections to brain stem motor centers and spinal cord.

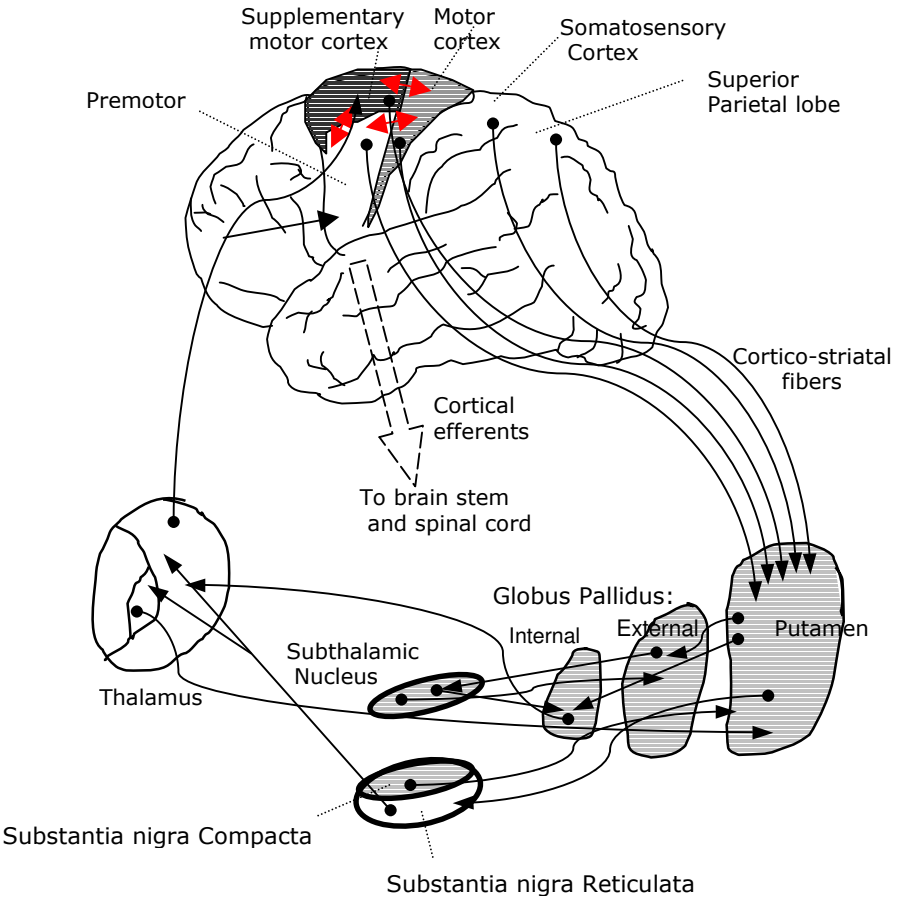

Figure 2.1: Anatomical basis for motor functions of basal ganglia

The striatum (STR) serves as a major target for the inputs from cortex to BG. Striatal output projections form two distinct parallel channels within the cortico-striato-pallidal pathways of BG. These projections are termed as direct and indirect pathways due to their effect on their target nuclei, namely thalamus. The direct pathway is formed by the inhibitory projections from the neurons of striatal output to neurons in the GPi.

Activation of striatal neurons inhibits neurons in GPi, which in turn disinhibit thalamic nuclei. Conceptually, the direct pathway can be seen as a normally–closed movement "gate". This gate is opened by the striatal activity that inhibits Pallidal output allowing emergence of movement. The indirect pathway is formed by inhibitory projections to GPe, which is thought to have an opposite effect to that of GPi neurons in the direct pathway. Activity in the indirect pathway tends to increase the activity of GPi cells, and therefore closes the "gate," via disinhibition of the Subthalamic nucleus. These pathways may be involved in modulating movement parameters (Contreras-Vidal & Stelmach 1996).

Striatal neurons consist of two kinds of dopamine receptors: D1 and D2 (Clark et al 2005). The direct pathway is activated when D1 receptors are activated by dopamine signals from SNc. Similarly, the indirect pathway is activated when D2 receptors are activated. Further, increase in striatal dopamine shifts the balance towards direct pathway, thereby increasing overall motor activity. Thus the indirect pathway is the normally active pathway. The balance is switched just before movement onset, when dopamine release to striatum activates the direct pathway (Clark et al, 2005). Fig 2.2 shows the functional anatomy of the basal ganglia.

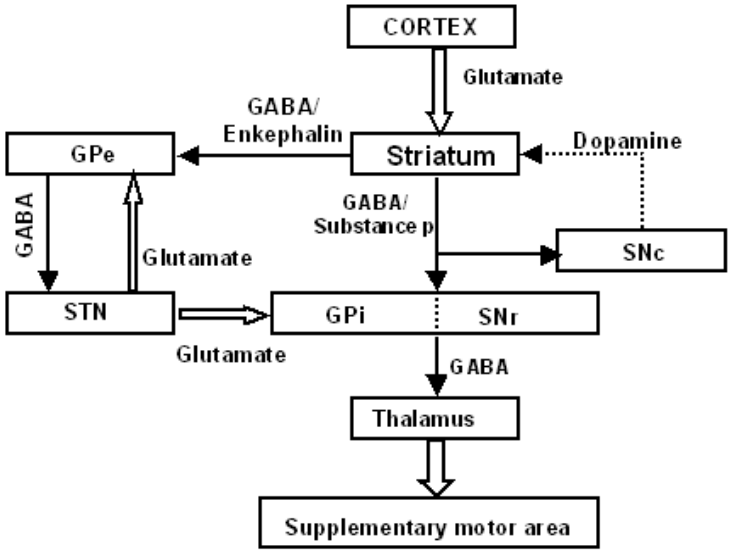

Figure 2.2 Functional Anatomy of the Basal Ganglia.

3.0 Dopamine, Reward Signaling and Reinforcement Learning

The classical theory of the function of dopamine has been the 'anhedonia hypothesis' proposed by Wise (1982). This hypothesis suggests that dopamine represents the hedonic qualities of natural reinforcers to brain systems responsible for behavioral control. These theories derive strength from accounts that addictive drugs exert their effects by primarily affecting the dopaminergic system. This notion is also supported by Brain Stimulation Reward (BSR) experiments in which animals choose to receive electric stimulation around the dopamine-related circuitry, even preferring such stimulation over natural reinforcers like food or water (Daw, 2003).

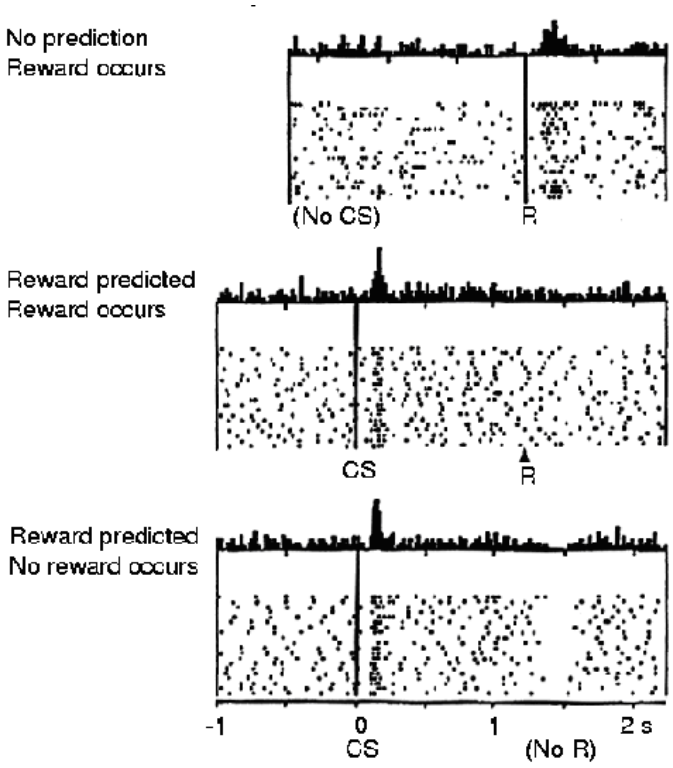

Fig. 3.1 Response properties of dopamine neurons (from Schultz et al. (1997)).

Mesencephalic dopamine neurons are observed to respond to natural rewards and novel or unexpected stimuli (Schultz, 1998). However, the observation that dopaminergic neurons respond to natural rewards is only an approximate description of their function. The activity of these neurons seems to represent something subtler: they even respond to stimuli that are *predictive* of reward. For example, in their work on primates, Schultz and colleagues (1997) recorded responses of dopaminergic cells in Ventral Tegmental Area to natural rewards (juice). A Conditioning Stimulus (CS – bell) precedes presentation of reward (R) (Fig. 3.1). In early stages of learning, when the R-CS association is not yet developed, dopaminergic neurons fire soon after the reward is presented (Fig. 3.1 - top panel). Once the R-CS association has taken place, dopaminergic neurons fire right after

the occurrence of CS; there was no change in firing rate on actual delivery of reward, R (Fig. 3.1 - middle panel). However, when the reward delivery is omitted, the firing rate of the neuron dropped at the instant when the reward is expected (Fig. 3.1 - bottom panel) (Mirenowicz and Schultz, 1994; Schultz et al. 1997).

These experiments suggested that dopamine response was not related to reward *per se*, but to the prediction of future reward. Dopamine neurons are activated by rewarding events that are better than predicted, remain unaffected by events that are as good as predicted, and are depressed by events that are worse than predicted. Thus, to put it more precisely, dopamine signal seems to represent the *error* between predicted future reward and actual reward (Schultz et al 1997).

The observation that midbrain dopamine signals represent the error between predicted future reward and actual reward marks perhaps the greatest progress in our understanding of BG. Interestingly, it was also observed that a sophisticated quantity like 'the error between predicted future reward and actual reward' has a close parallel to an analogous quantity known as Temporal Difference (TD) error in RL terminology (Sutton and Barto, 1998). It presents a possible scenario of BG as an implementation of RL machinery, that takes the dopamine signal from SNc, processes it, and broadcasts appropriate modulatory signals to the sensory-motor cortical pathways that form the neural substrates of S-R learning (Fig. 2.1). To add strength to such a perspective, let us discuss some key RL concepts and consider them in relation to BG function.

3.1 Dopamine and Reinforcement Learning:

Although early research on BG regarded these nuclei as being involved predominantly in motor function, later work recognized their importance to phenomena related to cognition, learning and memory. Memory is broadly classified into two prominent forms: 1) procedural memory (skills, habits, Stimulus-Response (S-R) form of learning etc) and 2) declarative memory (memory of facts, events etc) (Squire et al. 1996). Two memory systems in the brain are thought to form the neural substrates to the above forms of memory: basal ganglia for the S-R form of memory and the medial temporal lobe system including hippocampus for declarative memory (Squire et al. 1996).

Laying down of S-R form of memories is described by a form of conditioning known as instrumental conditioning, by which responses that are rewarding are reinforced and those that are unrewarding are attenuated. Thus instrumental conditioning is concerned with ways in which animals learn to predict and respond to important events in their environments such as the delivery of appetitive and aversive stimuli (food/juice and electric shocks, respectively) (Schultz et al, 1997). Instrumental conditioning is also closely related to RL, which studies how agents can choose their actions so as to maximize rewards (or minimize error) (Sutton & Barto, 1998).

To appreciate the challenge faced by an animal struggling to discover rewarding responses to environmental stimuli, let us return to a machine learning perspective and contrast RL with another form of learning such as supervised learning. In supervised learning, the desired response to a stimulus is explicitly available to the agent; the actual

response of the agent is compared to the desired response and the error is used to correct the agent's S-R map appropriately. No such explicit desired response (the "teacher") is available in case of RL. The agent has to explore the space of possible responses to a stimulus; responses that receive rewards from the environment are selectively reinforced. In an RL framework, this exploration is performed by a module known as the Explorer, which, however, can have a variety of realizations depending on the problem at hand.

Learning S-R maps using reward information would have been facile but for the need to explore the space of responses or actions. But the problem is made harder by another important and realistic constraint on reward schedule. In a natural setting, often rewards are delivered after the animal performs a sequence of actions. It is not easy to ascertain which of these past actions have contributed to reward delivery and to what degree. The need to evaluate past actions in terms of their relevance to future rewards is known as the *temporal credit assignment* problem. In an RL framework, the agent solves this problem by developing an internal model of this evaluation known as a Critic, which estimates the total expected future reward - a quantity known as Value function, *V(t)* - for the agent in its current state.

The evaluations of the Critic, and the perturbations of the Explorer are used to train the "S-R map", a module termed the Actor in RL jargon. Thus, Actor, Critic and Explorer are the key executive components of RL machinery.

The natural next step in modeling BG would be to look for neural analogues to Critic, Explorer, Actor and other key components of RL, so as to render our understanding of

BG complete. A lot of modeling effort has been directed to describe BG function using RL concepts (Montague et al, 1996; Schultz et al, 1997; Houk et al, 1995; Suri and Schultz, 1999; Daw & Touretzky, 2000; Frank 2005). We now describe some key ideas that have emerged from this line of study.

4.0 Computational Models of Basal Ganglia

Although early research implicated the role of the basal ganglia in motor function, later work also recognized its importance to phenomena related to cognition, learning and memory. In addition, damage to the basal ganglia is associated with complex neuropsychiatric cognitive and behavioral disturbances, reflecting the wider role of these nuclei in the diverse functions of the frontal lobes (Stout & Johnson 2005). A major part of modeling literature on BG pertains to involvement of BG in motor function and movement disorders (Chesselet & Delfs 2003).

Although enormous progress has been made in terms of anatomy, pathology, electrophysiology, and imaging studies related to the BG, a comprehensive understanding of the contribution of these nuclei to behavioral control still remains elusive. There is indeed a significant amount of computational modeling literature on BG, but most models tend to focus on only one or two functions of the basal ganglia. There is a great need for unifying functional models that integrate all the functions of BG in a single framework. From reviews of computational models of BG (Prescott et al, 2002, Houk et al, 1995) it appears that most BG models are exclusive and capture specific functional

roles. For example, there are models that describe the role of BG in *action gating* (Contreras-Vidal & Stelmach, 1995); in *action selection* between competing actions (Redgrave et al, 1999b, Berns & Sejnowski, 1995); in sustaining *working memory representations* (Houk et al., 1995); in s*equence learning* (Bapi & Doya, 1998; Berns & Sejnowski, 1998), and most importantly in *RL* (Montague et al, 1995; Schultz, 1998; Barto, 1994). Buhusi & Meck (2005) review the role of BG in *timing also.* An immense challenge that lies ahead of BG modelers is to forge the many exclusive albeit useful insights embodied by the models noted above into a single, integrated framework so as to construct a unified picture of BG function and show that the BG nuclei harness the reward information arising from dopaminergic signaling and use it to conduct their manifold operations.

4.1. RL models of Basal Ganglia:

It was mentioned above that activity of midbrain dopaminergic neurons represents the discrepancy between predicted and actual rewards, a quantity referred to as TD error in RL terminology (Schultz, 1998). Houk, Adams, and Barto (see Houk et al, 1995) were perhaps the first of several authors to suggest that something akin to an actor-critic learning system may be operating in the BG. Montague and colleagues (Montague, Dayan, & Sejnowski, 1996; Schultz et al., 1997) have proposed a computational RL model to explain the dopaminergic neural activity patterns observed in the experimental studies of (Schultz, 1998). An outline of the model is described below.

Consider the experimental setup of (Schultz, 1998) in which the animal is presented with a Conditioning Stimulus (CS) ("bell") followed by an Unconditioned Stimulus (US) ("food reward") after a delay. The animal is repeatedly presented with CS-

US pairs and activity of dopaminergic neurons is monitored. Consider that the time within a trial is measured using the discrete time variable *t*, which falls in the range $0 \le t \le T$. Let v*(t)* represent the activity of neurons that estimate total expected future reward based on the stimulus *u(t)*, and let r(t) represent the reward. Sutton and Barto (1990) suggested that the variable v*(t)*, which is the prediction at time *t* of the total future reward that will result, may be defined as.

$$\mathrm{v}(t) = \left\langle \sum_{\tau=0}^{T-t} \mathrm{r}(\mathrm{t}+\tau) \right\rangle \tag{4.1.1}$$

where the $\langle \bullet \rangle$ denotes an average over trials. It is assumed that v(t) depends not only on current stimulus, but on stimulus history. Thus, for the case of a single time-dependent scalar stimulus u(t), we write this dependence as,

$$\mathrm{v(t)} = \sum_{\tau=0}^{t} \mathrm{w}(\tau)\mathrm{u}(\mathrm{t}-\tau) \tag{4.1.2}$$

The stimulus vector u, is a tapped delay line representation of the stimulus history with each element u(t) of u being 1 if the stimulus is presented at time t and 0 otherwise. Such a representation allows the models to learn the temporal relationship between stimulus and reward. Dopaminergic neural activity, denoted by δ(t), is the difference between total expected and actual future rewards, it may be written as,

$$\delta(t) = \sum_{\tau=0}^{T-t} r(t+\tau) - v(t) \tag{4.1.3}$$

However, to calculate the quantity δ(t) at time t, the animal has to have access to future rewards r(t+τ), for $\tau > 0$, which is not possible. Therefore the expression on the right side

of (4.1.3) is substituted with an approximation as follows. Firstly, the summation on the RHS of (4.1.3) may be written as,

$$\sum_{\tau=0}^{T-t} r(t+\tau) = r(t) + \sum_{\tau=0}^{T-t+1} r(t+\tau+1) \tag{4.1.4}$$

Now, the summation on the RHS of (4.1.4) may be approximated by v(t+1), since it (the summation) is total actual future reward. Therefore, δ(t) in (4.1.3) may be expressed as,

$$\delta(t) = r(t) + v(t+1) - v(t) \tag{4.1.5}$$

This error signal is used to train the weights of (4.1.2) and improve the estimate of v(t) as follows,

$$\Delta w(\tau) = \varepsilon \delta(t) u(t-\tau) \tag{4.1.6}$$

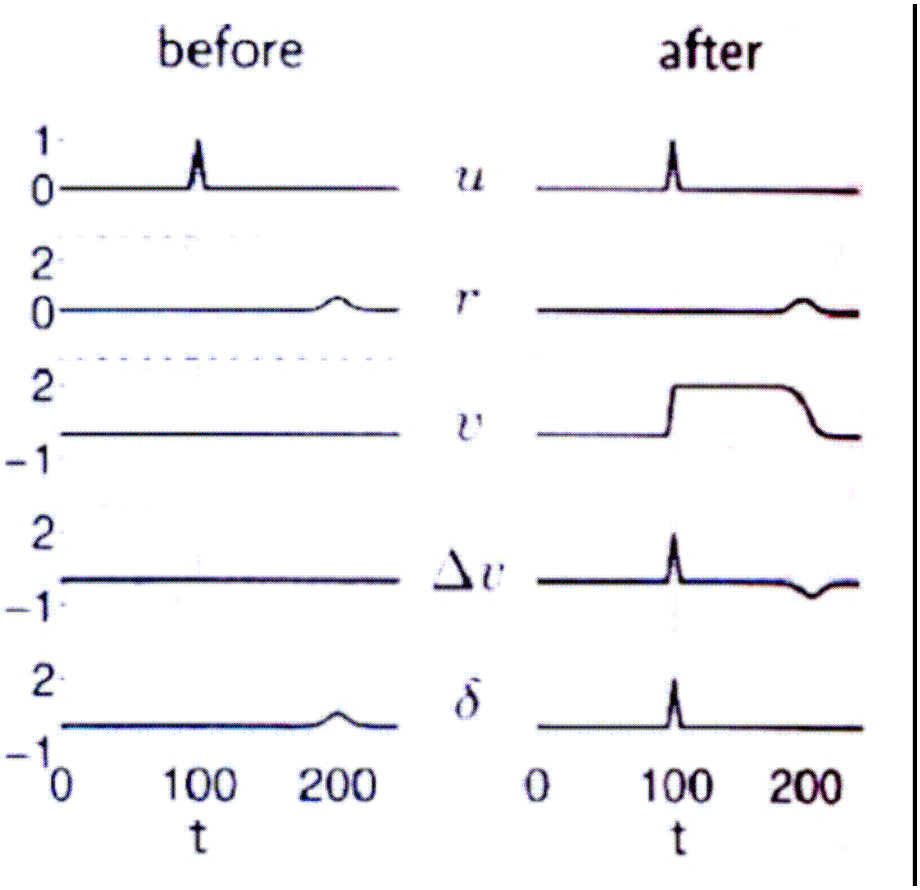

Fig. 4.1 Time series of the stimulus, reward, prediction of future reward, derivative of prediction of future reward, and temporal difference error, before and after learning (from Dayan and Abbott, 2001).

Let us now look at the simulation results of the CS-US pairing trials on the above system of equations (4.1.2 – 4.1.6). Fig. 4.1 shows the temporal profiles of relevant quantities, v(t), u(t), $\delta(t)$ and r(t) before and after "conditioning." Note that activity peak in $\delta(t)$ coincided with the time of occurrence of US before conditioning, and with the time of occurrence of CS after conditioning. Thus activity of mesencephalic dopamine cell is modeled effectively by the TD error signal, $\delta(t)$.

The model formulation described above (eqns.(4.1.2–4.1.6)) is akin to the model of Montague et al (1996). In that model, the dopamine neuron is assumed to receive input that informs about the rate of change of total future reward, $v(t) - v(t-1)$, and also reward information, r(t), from external world. The dopamine cell combines these two signals $(v(t) - v(t-1) + r(t))$ to estimate TD error, $\delta(t)$. The model of Montague et al (1996) is a model of dopaminergic cell responses and not a BG model. Therefore, no anatomical substrate of the value function, v(t), which is modeled by the Critic, or the third key RL component, the Explorer, are specified in that model.

Several authors have suggested that the striatum plays the role of the Critic in BG (Houk et al, 1995; Suri and Schultz, 1998; Contreras-Vidal and Schultz, 1999). Striatum receives extensive inputs from a number of sensory motor cortical areas. Particularly, each motor cortical area projects to a topographically distinct region of caudate and putamen. Since striatum also receives dopaminergic projections from SNc, it is rightly placed to implement the computation of (4.1.6), viz, dopamine-modulated plasticity of cortico-striatal connections.

Thus though there is a vast body of literature on applying RL concepts to BG function, there is no consensus on how, if at all, the RL machinery can be mapped – component by component – onto BG anatomy, and how such a mapping can explain the complete repertoire of BG functions (Joel et al, 2002; Worgotter and Porr, 2005).

5.0 Exploratory Behavior

An animal has to forage for food often in an uncertain, unknown environment. Two neural systems are thought to mediate exploratory behavior – one based on hippocampus and the other based on BG (Packard & Knowlton 2002). The role of hippocampus in spatial navigation abilities of rats has been studied extensively. Several studies have reported existence of place cells in rat hippocampus that are activated when the animal is located at a certain place in a familiar spatial environ (Packard et al 1989). In one experiment, rats were trained to go from a fixed starting position towards a baited arm (e.g., arm pointing to the West) in a T-maze (Packard and McGaugh, 1996). After several days of training, the maze was rotated by 180 degrees. The aim is to see if the animal shows evidence of place learning, and goes towards the same absolute direction (West), or exhibits Stimulus-Response (S-R) learning, makes the same body turn and goes in the wrong absolute direction (East). In other words, in place learning, the animal represents the target in a visuospatial coordinate system; in S-R learning the encoding is in motor coordinates, in terms of body position. After 8 days of training, most animals exhibited place learning, but after 16 days of training, majority exhibited S-R form of learning. Functional lesioning of dorsolateral striatum on 16^{th} day made the animals exhibit place

learning as opposed to S-R learning. Therefore, even though place learning is preserved, the animal switches from place learning strategy to S-R strategy on prolonged training. These and other experiments suggest that BG are involved in S-R form of navigation.

The involvement of dopaminergic activity in foraging behavior of bees has been studied (Scheiner et al, 2002). A model of bee foraging based on predictive Hebbian learning and dopamine neurons is presented by Montague et al (1995). In this model, the simulated bees follow a simple foraging strategy: if the dopamine signal is sufficiently high ('above baseline'), the organism stays on course, otherwise (dopamine cell activity is 'below baseline'), the organism tumbles randomly, a form of motion known as klinokinesis. However, what is the neural mechanism that drives the organism on its random tumble? There is no answer to this question in (Montague et al 1995). Although exploitation and exploration are equally important in an RL framework, literature dealing with the role of BG in RL seems to focus mainly on the reward signal – its chemical messenger, its anatomical site, and its consequences in learning etc. – but only present a summary treatment of exploration. It is often said that the activity of the dopaminergic cells of the SNc and/or the VTA indicate reward (Montague, 1995). But which part of BG generates the stochastic signal necessary for exploration?

Daw et al (2006) also note that while there is considerable clarity on the anatomical sites of exploitation, neural substrates of exploration are relatively unclear. In an imaging-based study with human subjects playing 'four-armed bandit' game, a RL game with a good blend of exploration and exploitation, Daw et al (2006) observe that frontopolar

cortex and intraparietal sulcus are preferentially active while the subjects are engaged in exploratory activities. The two cortical areas just mentioned may be the cortical sites supporting exploratory decision-making. But, since the other RL components associated with BG function have been identified within the BG circuit – TD error in SNc, Critic in Stiatum etc - it is surprising that no corresponding BG nucleus (or nuclei) has been mentioned as a subcortical base for exploratory behavior.

We had earlier suggested that the STN-GPe loop inside the BG circuit is rightly placed to support exploratory behavior (Sridharan et al 2006). In RL models, exploration is always modeled by stochastic components. In biological terms, only a neural system that is capable of producing complex spiking activity can probably be qualified to serve as an explorer. The STN-GPe layers which form an excitatory-inhibitory pair of neuronal layers, are known for their complex spiking activity in intact BG and a loss of this complex activity is observed in dopamine-deficient or Parkinsonian conditions (Nini et al 1995; Bergman et al, 1994; Brown et al, 2001).

5.1 The STN-GPe loop layer as a source of Stochasticity

Plenz and Kitai (1999) on the basis of their studies of basal ganglia organotypic tissue cultures have proposed that correlated activity can arise in both STN and GPe structures and is caused by the interaction between the two structures rather than being driven by an external source. Terman et al (2002) propose that a combination of weakened intra-GPe connections and strengthened striatal input sets the stage for synchronous STN-GPe oscillations and correlated rhythmic STN output. There is a dearth of precise anatomical information regarding the spatial organization of GPe-STN and STN-GPe projections and

whether the two nuclei project on each other in a reciprocal or out-of-register manner. Hurtado et al (1999) recorded neuronal activity from awake Parkinson's patients and observed some paired recording sites within the GPi that showed periods of transient synchronization. Bergman et al (1998) reported dynamic synchronization of pallidal activity in MPTP treated monkeys. Recent experimental studies have revealed prominent low-frequency periodicity (4-30Hz) of firing and dramatically increased correlations among neurons in the GPe and the STN (Bergman et al 1994; Nini et al 1995; Magnin et al 2000; Raz et al, 2000; Brown et al, 2001). Experimental studies of activity in the STN and the GPe revealed that under dopamine depleted circumstances (analogous to Parkinsonian conditions), activity of these nuclei exhibited, though not much reduction in firing rate, a dramatic increase in correlations among neurons (Bergman et al, 1994; Brown et al, 2001). In modeling studies, correlated activity of neurons of the STN-GPe loop has been functionally linked to Parkinsonian tremor frequencies (Terman et al, 2002) and to Parkinsonian handwriting distortions (Gangadhar et al 2007a).

Complex activity of STN-GPe loop in normal BG, and its loss in Parkinsonian conditions has been attributed a deep functional significance, and is interpreted as a source of the stochastic exploration required by RL (Sridharan et al, 2006). The model of Sridharan et al (2006) describes a simulated Morris water pool experiment, wherein a virtual rat explores for a hidden platform with the help of visible landmarks. When the platform (i.e. the set of landmarks associated with it) was not within the view of the agent, the STN-GPe part of the model exhibited uncorrelated activity, reflecting exploratory behavior.

When the platform (i.e. its associated landmarks) falls within view, the STN-GPe activity dramatically switches to correlated activity.

Discussing possible roles of various neuromodulators (dopamine, serotonin, norepinephrine and acetylcholine) in brain function seen from an RL perspective, Doya (2002) hypothesizes that: (i) Dopamine represents the global learning signal for the prediction of rewards and reinforcement of actions, (ii) Serotonin controls the balance between short-term and long-term prediction of reward, (iii) Norepinephrine controls the balance between wide exploration and focused execution, (iv) Acetylcholine controls the balance between memory storage and renewal. Specifically, in support of the hypothesized role of norepinephrine in exploration, Doya points out that noradrenergic neurons in the Locus Ceruleus (LC) are activated in emergency situations (Doya, 2002). Further, it is known that phasic response in the LC neurons at the time of stimulus presentation is correlated with a high accuracy of response (Aston-Jones et al., 1994). Other authors have also suggested a link between norepinephrine and the exploration-exploitation problem (Usher et al, 1999). There is also evidence to connect norepinephrine with the level of activity in the Globus Pallidus (Russel et al, 1992). Such perceptions are much in tune with the idea of attributing to the STN-GPe loop, a role in exploratory behavior (Sridharan et al, 2006).

A main theoretical problem concerns exploratory behavior and the trade-off between exploring to get new information and exploiting existing knowledge in order to get reward. Studying how animals choose to balance exploration and exploitation is a rich field of investigation (Montague and Berns, 2002). It has been suggested that activity of the dopamine system that is not associated with prediction errors for reward, might be

associated with ensuring appropriate exploration (Suri and Schultz, 1991; Suri 2002; Kakade and Dayan, 2002). The close relationship between dopamine and temporal difference error in reinforcement learning has laid bare a new and powerful connection between animal and artificial decision-making systems.

6.0 Motor Preparation

In their classic EEG studies of voluntary motor action, Kornhuber and Deecke (1990) found slow negative shifts in cortical potential much before the initiation of movement. This potential, termed the Bereitschafts Potential (BP), is believed to signify the premovement preparation of motor cortical areas. Careful current dipole source analysis of BP has identified the SMA as a key player (Lang et al, 1991). However, preparatory activity corresponding to movement direction has been found in many other brain areas including M1 (Georgopoulos & Grillner, 1989), premotor cortex (Kubota and Hamada, 1978), prefrontal cortex (Kubota and Funahashi, 1982), the parietal cortex (Crammond and Kalaska, 1989), and BG (Alexander, 1987). An interesting functional definition of motor preparation emerges out of primate experiments by Churchland et al (2006). This group hypothesizes that preparation is a process by which activity of the motor cortical neurons, random and variable in early stages of preparation, is progressively pushed into a limited region of the state space that is specific to a given movement. Data from premotor cortical neurons from primates appears to confirm their hypothesis (Churchland et al, 2006). However, it appears that compared to other motor cortical areas, SMA has a predominant role in motor preparation.

6.1 SMA and Motor preparation: SMA seems to compete with several other motor areas as a primary source of motor preparatory signals. Single cell recordings in primates revealed more marked preparation-related changes in SMA neurons than in neurons of M1 (Tanji, 1994). The question of 'which area comes first – SMA or M1?' can be resolved if it can be shown that preparatory activity in SMA neurons precedes similar activity in M1. It has been shown that SMA neurons exhibiting preparatory activity can be identified to project to M1 (Tanji 1994). Contrarily, it was also established that M1 neurons that exhibit preparatory activity receive inputs from SMA and not from thalamus or parietal cortex (Aizawa and Tanji, 1994). Such studies strongly implicate a role to SMA in motor preparation. However, perhaps SMA may not be solely responsible for motor preparation. Its preparatory action might involve interactions among subcortical structures like basal ganglia, which are often implicated in motor timing functions: Interaction between the SMA and the basal ganglia is believed to play a crucial role in learnt motor sequences (Cunnington et al, 1995, Bapi et al., 2006). It has been suggested that phasic activity of the basal ganglia may act as a "reset" signal to the SMA clearing the traces after one movement and preparing it for the consecutive movement (Georgiou et al, 1993).

From the above account, we understand that motor preparation is effected by two-way interactions between BG and SMA. A similar view of preparation had emerged out of a computational neuromotor model of handwriting generation (Gangadhar et al 2007b). The model is inspired by Hollerbach's (1981) oscillator theory of handwriting, according to which handwriting may be regarded as superimposed motion of two oscillatory

processes – one vertical and the other horizontal. Handwriting shapes can be generated by modulation of various parameter of oscillation like phase, amplitude at isolated instants. Gangadhar et al (2007b) describe a network of neural oscillators that can learn arbitrary strokes by resolving stroke velocities in a Fourier-like fashion, in terms of oscillatory activities of neurons in the network. Accurate stroke execution depends not only the 'weights' of the network, but critically on the initial phase of the oscillators. The 'basal ganglia' module in the model sends preparatory signals to the oscillatory neurons and initializes their phases, by driving them from random initial phases to a "standard phase state". Such a view of motor preparation strongly echoes the view of Churchland et al (2006) who observe that activity patterns of dorsal premotor (PMd) neurons move from random initial state to an 'optimal subspace' which refers to a confined set of states.

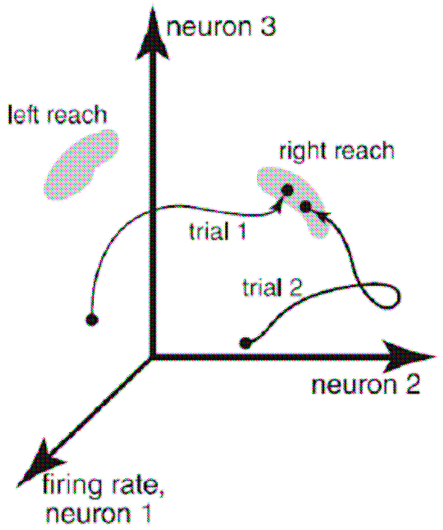

Fig. 6.1 Illustration of how pre-motor activity might settle over time. Activity is represented in a high-dimensional space, with each neuron's firing rate providing an axis. Activity is initially variable, and near baseline (one dot per trial). Following target onset, activity settles (curved paths) to a subspace of states appropriate for the desired movement (shaded area) (adapted from Churchland et al, 2006).

As an extension to the motor preparation studies presented in (Gangadhar et al 2007b), our group had recently studied preparation in Parkinsonian conditions (unpublished results). In the model, we identify the drive signal from BG to SMA in the model with the phasic dopamine burst which is known to occur in the beginning of or before movement. Since dopamine-deficiency is a hallmark of Parkinson's disease (PD), we simulate PD conditions in the model by weakening the drive signal meant to prepare the neural oscillators. As drive signal (scaled by a factor known as 'drive factor', γ_{df}) is weakened, preparation takes longer and longer; when γ_{df} drops below a critical value, preparation never terminates and movement is never initiated. This failure to prepare the motor cortex for movement resembles the difficulty faced by PD patients with voluntary control. Particularly, it provides an interesting explanation to the freezing phenomenon (Giladi et al, 1992) of PD, which we suggest may be regarded as a case of failed motor preparation.

7.0 BG, Prefrontal Cortex (PFC) and Working Memory

Clinical importance of the fronto-basal ganglia circuitry emerges from the involvement of these circuits in a range of neuropsychiatric disorders like schizophrenia, attention deficit hyperactivity disorder etc (Cohen et al 2002). Prefrontal areas have a recognized role in cognition, goal-directed behavior, working memory, and attentional functions (Gabrieli et al, 1995; Knight et al, 1995). Goal-directed behavior requires that the goal-related information is stably held in the mind while the individual is engaged in actions that help in attainment of the goal. PFC has been identified as a key player in this process because this cortical area has been found to be preferentially activated in tasks that involve goal-

seeking. Furthermore, damage to PFC leads to impairments in goal-seeking (Cohen et al, 2002)

Although PFC fulfils the need for a mechanism for maintenance of goal-related information, it leaves two questions unanswered: 1) how long should the goal-related information be held in PFC? 2) by what mechanism is updating of information in PFC engendered? It has been suggested that dopaminergic projections to PFC from Ventral Tegmental Area (VTA) perform this gating of information in PFC (Cohen et al, 2002). According to this proposal, in the absence of phasic dopamine release, activity of PFC remains robust against perturbing afferent inputs. Phasic dopamine burst opens the gate and permits updating of goal-state in PFC (Montague et al 2004). O'Reilly and Frank (2006) present a model of working memory involving PFC and BG in which the gating of working memory by dopaminergic projections to PFC is described within the framework of RL. The reward-related information in dopamine signal is used to decide which information is maintained over time and which information is allowed to be updated in PFC.

Disturbances in dopaminergic transmission to PFC is linked to pathogenesis of schizophrenia (Montague et al 2004). For nearly half a century, schizophrenia has been believed to be a hyperdopaminergic state. The fact that drugs that block dopaminergic transmission ameliorate delusional symptoms of schizophrenia, and that dopamine agonists reproduce some of schizophrenia symptoms, lent support to this belief. However, later work demonstrated that the link between dopamine and schizophrenia is more complicated than that. A more recent assessment is that schizophrenia is associated with reduced dopamine in PFC and increased dopamine levels in striatum. By simulating

reduced dopaminergic gain in PFC using computational modeling, it was possible to reproduce symptoms of schizophrenia (Servan-Schreiber et al 1990).

8.0 Timing

Coordinating the relative timing of multiple streams of processing is crucial in both motor performance and sensory perception. Temporal processing in biological systems occurs over a range of time scales and is broadly classified into 3 categories: 1) circadian timing, which corresponds to durations of the order of days, and handled by brain structures like suprachiasmatic nuclei, 2) interval timing, which corresponds to durations in the range of seconds to minutes, and coordinated primarily by corticostriatal interactions, and 3) millisecond timing, which obviously corresponds to millisecond durations, controlled by the cerebellum (Buhusi and Meck, 2005). Apart from timing aspects, contributions of the corticostriatal and cortico-cerebellar systems have been distinguished with respect to motor skill learning (Doyon et al, 2003).

Recent data indicate that time might be represented in a distributed manner in the brain and that telling the time is a matter of detecting coincidental activation of different neural populations. Interval timing depends on the intact striatum (Malapani et al 1998). An impaired ability to process time in the seconds-to-minutes range is found in patients with disorders that affect the dopaminergic pathways like Parkinsons Disease (PD), Huntington's disease and Schizophrenia. PD patients show the scalar property when under L-dopa but not when tested off-medication (Malapani et al 1998). They are unable to time two durations independently; the reproduced criteria for the two criterion

durations tend to migrate towards each other. This migration is eliminated and accurate timing reinstated after stimulation of the Subthalamic Nucleus. They also show a poor timing of motor actions. Preservation of the scalar property after cerebellar lesions supports the view that the striatum and cerebellum are involved in different aspects of timing and time perception. As mentioned earlier, the cerebellum has been charged with millisecond timing and the BG with interval timing.

The role of basal ganglia in 'interval timing' appears to emerge from the dynamics of thalamocortico- striatal loops. In the Striatal Beat Frequency (SBF) model (Matell and Meck, 2004), a model that highlights the timing function of BG, cortical oscillators are assumed to increase synchrony just before movement onset and maintain the rhythm throughout the performance. The dopaminergic burst at trial onset could trigger the synchronization of cortical oscillators according to the SBF model (Buhusi and Meck, 2005). Striatal neurons are tuned to respond to specific patterns of cortical oscillations (Matell and Meck, 2004). Experience dependent changes in the cortico-striatal transmission are assumed to make the striatal neurons more likely to detect the specific pattern of activation of cortical oscillators at the time of reward delivery through cortico-striatal LTP & LTD (Buhusi and Meck, 2005).

If we accept the view that BG nuclei are substrates of RL machinery in the brain, then the involvement of BG in timing-related functions is only natural. Prediction of future reward, which is one of the key subproblems of RL, involves answering two questions: "how much?" and "how soon?" In the process of solving the temporal credit assignment problem underlying RL, BG naturally address the timing problem and learn the temporal relationships among the rewarding events, stimuli and actions.

9.0. BG and Action Selection

The proposal that the BG resolve the tie among competing actions is based on a growing consensus that a key function of these structures is to arbitrate between sensorimotor systems competing for access to the final common motor path. A computational hypothesis developed from this idea relies on the premise that afferent signals to the striatum encode the salience of 'requests for access' to the motor system (Redgrave, Prescott and Gurney, 1999b). Multiple selection mechanisms embedded in the BG could resolve conflict between competitors and provide clean and rapid switching between winners. First, the up/down states of the striatal neurons may act as a first pass filter to exclude weakly supported 'requests'. Second, local inhibition within the striatum could selectively enhance the activity of the most salient channels. Third, the combination of focused inhibition from striatum with diffuse (divergent) excitation from STN could operate as a feed-forward, off-center/on-surround network across the BG as a whole (see Mink, 1996). Lastly, local reciprocal inhibition within the output nuclei could sharpen up the final selections.

Using the action selection hypothesis as an organizing principle, Prescott et al, (2002) have proposed a new functional grouping based on selection and control circuits. The strength of this model has been tested by embedding it in the control architecture of a mobile robot equipped with a small repertoire of animal-like behaviors (see Prescott et al., 2002). This work confirmed that the simulated BG can provide effective action

selection in a real-world context requiring appropriate and timely behavioral switching. The robot model also provided an insight into the emergent consequences of abnormal dopamine modulation of action selection. For instance, reminiscent of some motor symptoms of Parkinson's disease, reduced dopamine was found to cause failures to select appropriate behavior or to complete behaviors once selected.

Recent studies have provided evidence for local inhibition within the striatum mediated either via local interneurons or by reciprocal inhibitory networks among the output cells themselves (Oorschot et al., 2002). Wickens (1997) investigated the dynamics of such local neighborhoods of striatal neurons using network models. Under varying assumptions of topology and size, it was observed that reciprocal inhibition will usually lead to a network dynamic of competition, that is, the most active neurons will tend to suppress activity in their less active neighbors. This research also explained the effects of simulated dopamine inputs, showing that under circumstances of low dopamine, the dynamics of the network changes from competition to co-activation (where activity is uniformly distributed within the local population of neurons), a pattern that could provide a model for the muscular rigidity seen in dopamine deficient Parkinson's patients.

Redgrave et al (1999a) contend that the short duration, short latency response of dopaminergic cells to unexpected presentation of behaviorally salient stimuli represents an important component of the processes that are responsible for reallocating attentional and behavioral resources in favor of unexpected salient events. It is presumed that such a burst produces a relatively non-differentiated wave of dopaminergic input to wide areas of the striatum. The authors (Redgrave et al, 1999a) state that the vertebrate BG has evolved as a central selection device, specialized to resolve conflicts between multiple

sub-systems that compete for access to limited motor or cognitive resources. Within this framework, selection operations selectively disinhibit the sensori-motor connections of 'winning' competitors, while at the same time maintaining or increasing the inhibitory control over 'losing' competitors. Another implicated function of the dopamine burst is that before a rewarding stimulus can be located and consumed, it is first necessary to interrupt ongoing behavior and switch attentional and behavioral resources to deal with the rewarding event. Such a role is substantiated by the discovery that unexpected novel or intense stimuli always elicit short-term dopamine bursts.

10.0 BG and fatigue

Fatigue refers to a state of exhaustion when the individual feels incapable of generating enough force to perform significant work. However, it must be distinguished from weakness in which the individual is actually unable to generate sufficient muscular force commensurate with the task at hand. This latter form of fatigue may be called 'muscular fatigue' or even 'peripheral fatigue'; it refers to actual inability of the muscle to generate force. It may be distinguished from 'central fatigue,' which refers to the subjective *feeling* of being exhausted. This central fatigue figures prominently in a syndrome known as the 'chronic fatigue syndrome' (CFS) which is characterized by, among other things, cognitive problems, sleep impairment, allergies and sensitivities, headaches, low grade fever etc. It is usually defined by presence of persistent and relapsing unexplained fatigue lasting for at least 6 months (Fukuda et al 1994). What is puzzling about CFS patients is that they need not be actually weak but only suffer from a constant feeling of weakness or fatigue. Chaudhuri and Behan (2000a) mention neurological disorders, other than CFS,

that are related to central fatigue. These include post-polio syndrome, post-viral syndrome, post Guillain Barre syndrome, multiple sclerosis, Parkinson's disease etc.

Some important defining features of CFS symptomology are (Chaudhuri & Behan 2000b):

1) CFS patients exhibit delayed motor conduction similar to that seen in multiple sclerosis patients
2) CFS patients are not able to fully recruit their muscles in spite of having an intact muscular system
3) They have an exaggerated perception of effort
4) They also exhibit reduced motor evoked potentials during exercise compared to controls

Transmagnetic Stimulation (TMS) studies with CFS patients revealed that the patients are not only not activating their muscles to the fullest extent, but that the reduced muscle activation seen was due to reduced central activation (Sacco et. al 1999). In addition to reduced motor cortical activity during movement, reduced premovement or preparatory activity was also observed in CFS patients (Starr et. al. 2000). These studies indicate that a key causative factor in CFS is reduced drive to the motor cortex.

Chaudhuri and Behan (2000c) hypothesize that the origins of central fatigue lies in the dynamics of BG circuitry. With arguments based on neuropathological data, these authors suggest that central fatigue arises due to "failure in the integration of the limbic input and the motor functions within the basal ganglia affecting the striatal-thalamic-

frontal cortical system" (Chaudhuri and Behan, 2000c). Elsewhere, Chaudhuri & Behan (2000a) describe voluntary work as a variable that depends jointly on applied effort, which depends on motivational input; and perceived exertion, which depends on sensory-motor feedback from the body. Central fatigue seems to be a case of impaired "perceived exertion."

The idea that fatigue arises due to failure in integration of limbic and motor inputs in BG is very much in line with the perspective of BG function developed in this review. So far, in this review, we have primarily focused on sensory motor aspects of BG function. However, the cortico-strio-pallido-thalamic pathways that course through BG nuclei are organized as parallel loops that are segregated based on their functions (Alexander et al., 1990, Hikosaka et al., 1999). According to the eminent classification of Alexander et al (1990), the loops are: 1) skeletomotor loop, 2) oculomotor loop, 3) associative loop and 4) limbic loop. Since these pathways are organized topographically, segregation of the loops is maintained throughout BG circuitry. The first two loops, the skeletomotor and oculomotor loops, as the names suggest, control musculoskeletal functions and eye movements respectively. The associative loop is involved in cognition, memory and attention. The limbic loop interacts with cortical and subcortical limbic areas like anterior cigulate cortex, amygdala etc. and is involved in motivational activities, homeostasis, visceral monitoring and control. The sensory motor functions and reward-processing as it is described in this review so far, is most relevant to the first two loops (skeletomotor and oculomotor). But it appears that understanding the involvement of associative and limbic loops is key to understanding the relationship between BG and fatigue.

To understand BG functions in limbic domain, we hypothesize an expanded picture of reward processing by BG. The essential picture of reward processing in BG presented so far is as follows: BG bind signals that represent natural rewards (food, juice etc) with neutral sensory stimuli, predict future rewards and use those predictions to choose rewarding actions. But viewing an action merely as rewarding or unrewarding is a narrow view of action and its implications. An important component seems to have been missed here. To perform an action, an animal has to spend energy; or it may have to incur risk. Therefore, choice of an action is based not merely on its intrinsic reward; the action is selected and executed only when the reward outweighs the metabolic cost and/or risk incurred by the animal by that choice. To be precise, since the actual reward or actual metabolic cost are not known to the animal before the action is performed, the animal probably bases its judgment by comparing *predicted* reward with *expected* metabolic cost and/or risk. We know that BG motor loops provide with reward predictions; we hypothesize that the limbic loop provides information regarding expected metabolic costs.

11.0 BG and Apathy

Apathy is usually defined as 'lack of feeling, emotion, interest or concern' (Levy & Dubois 2005). In terms of observable features, it is marked by a drastic reduction in voluntary or goal-directed behavior. Therefore apathy is a natural outcome of alterations in neural circuits - most importantly PFC and BG - that subserve voluntary actions. Lesions of PFC (Eslinger and Damasio, 1985; Fuster, 1997; Stuss et al, 2000) and of specific structures in BG (Bhatia and Marsden, 1994; Engelborghs et al., 2000; Ghika-

Schmid and Bogousslavsky, 2000) often result in apathy. Apathy, however, is not a simple unitary process: a variety of factors – cognitive, emotional etc. – can underlie apathy. Accordingly, Stuss et al (2000) group apathy types into three categories: 1) cognitive, 2) emotional and 3) behavioral. These categories are further associated with certain precise anatomical substrates in BG-PFC circuitry.

The emotional component of apathy is associated with orbital and medial PFC and the ventral striatum to which it is connected. Primate electrophysiology studies and imaging studies with humans indicate that the orbital and medial PFC is important to interpret the relative or contextual value of reward and use it as impetus for behavior (Thut et al., 1997; Tremblay and Schulz, 1999). As a consequence, lesions in orbital and medial PFC may lead to deficits in reward detection, and therefore to a reduction in voluntary actions, which may be interpreted as apathy.

Similarly the cognitive component is linked to lateral PFC and dorsal caudate nuclei (Levy & Dubois 2005). This aspect of apathy, alternatively described as 'cognitive inertia' is related to impaired goal directed behavior. Goal directed behavior involves a host of component functions like planning, working memory, rule-finding and set-shifting; these functions are preferentially impaired by lesions in lateral PFC (Goldman-Rakic, 1987; Fuster, 1997). Moreover lesions of dorsal caudate nucleus produce behavioral deficits, for example in delayed alternation tasks, similar to those obtained in case of lateral PFC lesions (Dean & Davis 1958; Iversen, 1979).

Thus, the emotional component of apathy seems to stem from inability to adequately sense and respond to presence of reward. The cognitive aspect arises from deficits in various component functions of goal-directed behavior. The third aspect of

apathy, the 'behavioral' aspect, also described as 'auto-activation deficit' (Levy and Dubois 2005), refers to a loss of spontaneous activation. Patients in this condition may prefer to sit quietly for extended periods without talking to anyone or taking any initiative. However, they may respond appropriately to external stimulation and produce relevant answers and actions.

In summary, it may be stated that apathy arises due to disruptions in fronto-basal ganglia circuitry. Further since it is related to deficits in reward processing, involvement of dopaminergic signaling may be expected. Therefore, not surprisingly, apathy is often observed in PD patients, and, further, marked differences in apathy may even be observed between 'ON' and 'OFF' states of PD patients (Czernecki et al., 2002). Thus, it appears that apathy and fatigue could be related to the disruption in the convergence of motivational and emotional information from the limbic pathways which project to the ventral striatum and the striosomal modules in BG. Matrisomal modules, on the other hand, seem to be receiving sensori-motor information from the cerebral cortex. BG are thought to be in the best position to combine the affective information into goal-directed behaviours (Houk et al. 1995).

12. Summary and Conclusions:

Drawing from existing literature on functional aspects of BG, in this review, we attempted to present a conceptual synthesis of the BG function. From this synthesis, the essence of BG function may be stated as follows: BG combine the sensory-motor context of an organism with reward information and pass on this combined information to motor

and prefrontal cortical areas for decision making. Most functions of BG seem to have their roots in this essential operation. Although there are no computational models at present for all aspects of BG function, a preliminary conceptual synthesis can prepare the ground for a formal modeling effort.

The functional position of the subcortical nuclei of BG with respect to the cortex may be illustrated in fig. 12.1. BG take sensory information from sensorymotor cortical areas, combine it with dopaminergic reward information (from SNc) and supply a result of the synthesis of these two signals (reward + sensory-motor) to control or decision making areas of the cortex (prefrontal areas and supplementary motor area). BG inputs to these areas act as a 'gate' that typically allows rewarding actions or disallows unrewarding ones. Further, when multiple actions compete for execution at the same time, the BG system acts as an arbitrator that resolves the competition by making use of dopaminergic reward information as a salience measure.

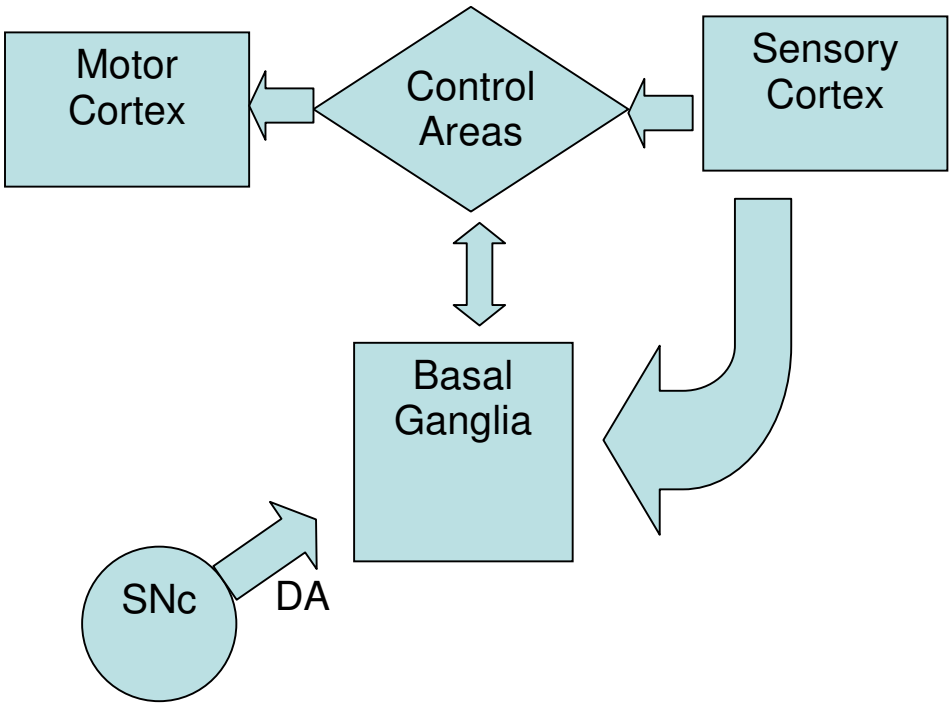

Figure 12.1: A simplified schematic for illustration the 'gating' function of BG. The position of BG with respect to sensory-motor cortical areas is shown. The Control areas include Prefrontal areas and Supplementary Motor Area. Though SNc is usually considered a part of BG it is shown outside BG to reveal the DA signal. Not all connections are shown for clarity of presentation.

The term 'gating' may be regarded as a coarse first-order description of BG function. Essentially BG combine sensory-motor context and reward information and appropriately inform, influence or modulate the 'control areas' (PFC areas and SMA), which is far more sophisticated than mere gating. Another instance of such influence or modulation is motor preparation, in which BG monitors SMA activity and sends preparatory drive to SMA before sequencing the next movement. The two-way interaction between Control areas (here SMA) and BG shown in fig. 12.1, provides the anatomical substrate for such a preparatory process.

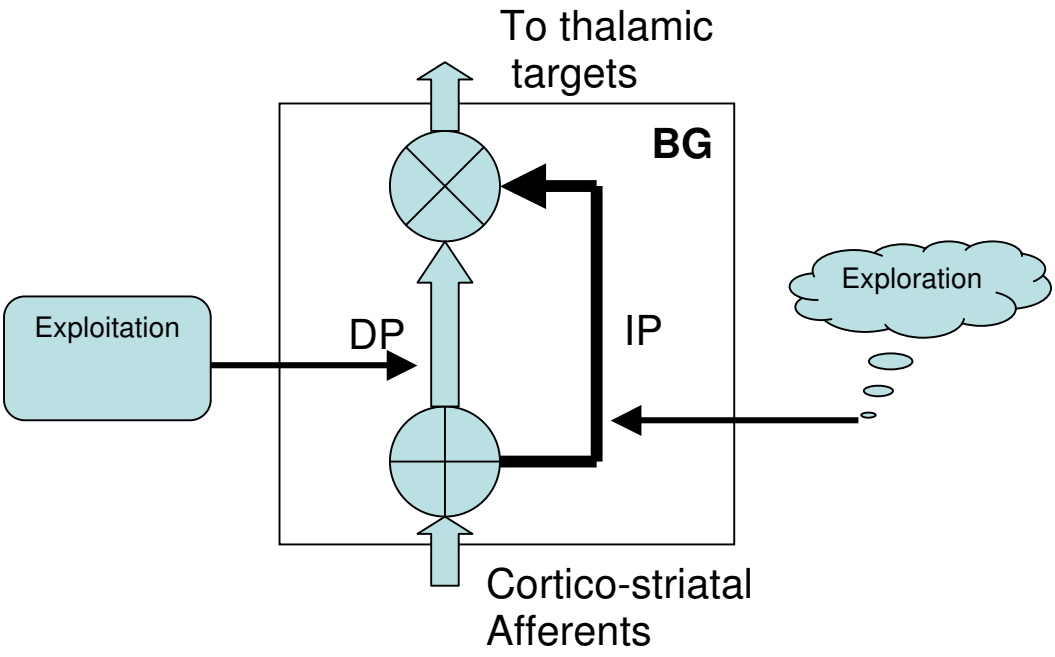

Figure 12.2: The Direct and Indirect Pathways of BG, hypothesized to subserve exploitation and exploration functions, respectively.

An agent engaged in reinforcement learning needs to switch between exploitation and exploration. Incorporating the idea that the Indirect Pathway (IP) consisting of the STN and the GPe has the machinery to generate the randomized signal necessary to drive exploration, we now have a picture of BG function in which the Direct and the Indirect Pathways subserve exploitation and exploration respectively (fig. 12.2). There have been several studies which suggest that loss of complex activity in the Indirect Pathway might be responsible for Parkinsonian tremor. Thus, unlike several earlier theoretical suggestions which consider the Indirect Pathway as playing a somewhat weaker role like, for example, providing contextual information, or focusing the GPi outputs, IP plays quite a significant role – a role that is exactly *complementary* and not just *opposite* (Frank 2005) to that of DP – in the perspective of BG function developed in this review.

While we endeavor to present a coherent conceptual synthesis of BG function, linking its multitudinous functions to its essential role of learning by reinforcement, we admit that the time is not yet ripe to translate this conceptual picture into a detailed and comprehensive computational model. It takes an enormous amount of modeling effort to translate the coherence that is now apparent at a conceptual level into a comprehensive, inclusive model. It is indeed a modeler's delight to be able to describe this 'mysterious' (to paraphrase Marsden's depiction of BG) system in perfect computational terms.

Even though the functional architecture of BG, in its relation to other key brain areas, as depicted in figs. 12.1 and 12.2, is interesting and compelling in its own right, it

must be noted that there exist radically different views of BG function in contemporary literature. As new experimental data is obtained, there is an attempt to add newer connections, and even modules to existing BG architecture. Such additions challenge earlier conceptions of BG function. They seem to demand a thorough revision of the matter from scratch, or an accommodation, if possible, of the new data into the preexisting framework.

For instance, Leblois et al (2006) organize the BG and related structures into two loops: the first consisting of cortex-striatum-GPi-thalamus-cortex, which is the same as the traditional Direct Pathway, and the second consisting of cortex-STN-GPi-thalamus-cortex which they term the hyperdirect pathway. The authors suggest that competition between these two loops is responsible for action selection. In another such radical proposal, Obeso et al (2006) place the GPe in a central position with cortex-STR-GPi and cortex-STN-GPi as two parallel pathways winding around GPe (fig. 12.3). The authors support their architecture mostly from experimental studies and there is no mention of reinforcement learning. It would be a nontrivial challenge to see if such an architecture can be shown to explain RL functions of BG.

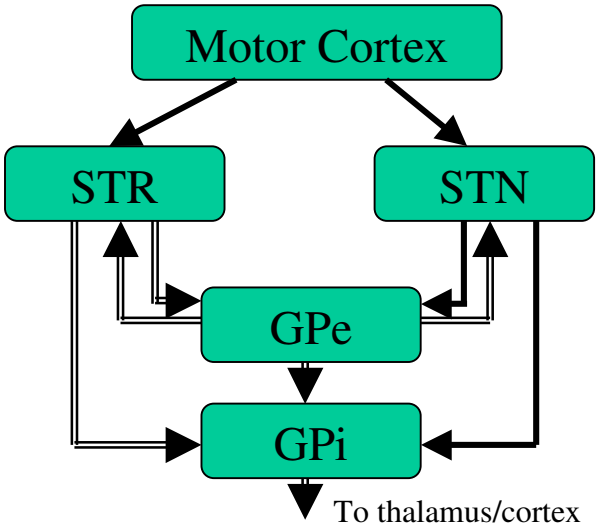

Figure 12.3: A schematic of BG architecture proposed by Obeso et al (2006). (redrawn based on (Obeso et al 2006)).

With so much rethinking going on about BG function, even after nearly 30 years of intense research, the subject appears more challenging than it has ever been. Nevertheless, what remains invariant under the tangle of conflicting suggestions is the essential view that BG is a network of subcortical structures that strongly influences decision-making in cortical control structures by processing the reward-related information in midbrain dopaminergic signals. All the heated debate is over the nature of detailed information processing that occurs in specific BG nuclei. But then, the devil, as the saying goes, is always in the detail.

Acknowledgments

The authors acknowledge the many useful discussions they had with Gangadhar Garipelli and Sridharan Devarajan on various topics related to basal ganglia modeling. This work is sponsored in part by a research grant from the Department of Science and Technology, India.

References:

1. **Aizawa, H. and J. Tanji** (1994) Corticocortical and thalamocortical responses of neurons in the monkey primary motor cortex and their relation to a trained motor task. *Journal of Neurophysiology*, **71**, 550-60.
2. **Alexander GE, M. D. Crutcher and M. R. DeLong** (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, prefrontal and limbic functions. Progress in Brain Research, **85**, 119 – 146.

3. **Alexander, G.E.** (1987) Selective neuronal discharge in monkey Putamen reflects intended direction of planned limb movements. *Experimental Brain Research*, **67**, 623-634.
4. **Aston-Jones, G., J. Rajkowski, P. Kubiak, and T. Alexinsky** (1994) Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *Journal of Neuroscience*, **14**, 4467-4480.
5. **Bapi, R. S. and K. Doya (1998).** A Sequence Learning Architecture Based on Cortico-Basal Ganglionic Loops and Reinforcement Learning. ICONIP'98, Kita-Kyushu, Japan, Oct 21–26, 1998.
6. **Bapi, R.S., K. P. Miyapuram, F. X. Graydon, and K. Doya (2006)**. fMRI investigation of cortical and subcortical networks in the learning of abstract and effector-specific representations of motor sequences, *Neuroimage*, **32**(2), 714-727.
7. **Barto, A.G.** *Adaptive Critics and the Basal Ganglia.* pp. 215-232. *In* **J.C. Houk, J. Davis, and D. Beiser** (ed.) *Models of Information Processing in the Basal Ganglia*, MIT Press, Cambridge, MA, 1995.
8. **Bergman, H., A. Feingold, A. Nini, A. Raz, H. Slovin, M. Abeles, and E. Vaadia** (1998) Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. *Trends in Neuroscience*, **21**, 32-38.
9. **Bergman, H., T. Wichmann, B. Karmon, and M.R. DeLong** (1994) The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of Parkinsonism. *Journal of Neurophysiology*, **72,** 507-520**.**
10. **Berns, G.S. and T.J. Sejnowski** (1995) A Computational Model of Local memory in the Primate Pallidal-Subthalamic Circuit. *Society for Neuroscience Abstracts*, **21**, 678.
11. **Berns, G.S. and T.J. Sejnowski** (1998) A computational model of how the Basal ganglia produce sequences. *Journal of Cognitive Neuroscience*, **10**, 108-121.
12. **Bhatia K. P. and C. D. Marsden** (1994) The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain*, **117**, 859-876.
13. **Bolam, J. P., Hanley, J.J., Booth A.C. and Bevan, M.D.** (2000), Synaptic organization of the basal ganglia, J. Anat. 2000 May; 196(Pt 4): 527–542.
14. **Brown, P. A. Oliviero, P. Mazzone, A. Insola, P. Tonali, and V. Di Lazzaro** (2001) Dopamine dependency of Oscillations between Subthalamic Nucleus and Pallidum in Parkinsons disease. *The Journal of Neuroscience*, **21**, 1033-1038.
15. **Buhusi, C.V. and W.H. Meck** (2005) What makes us tick? Functional and neural mechanisms of interval timing. *Nature Reviews Neuroscience*, **6**, 755-756.
16. **Chaudhuri, A. and Behan, P.O.** (2000a). Fatigue in Neurological disorders, *Lancet*, **179**, 34– 42.
17. **Chaudhuri, A. and Behan, P.,** (2000b), Neurological dysfunction in Chronic Fatigue Syndrome, *Journal of Chronic Fatigue Syndrome 6, 51-68*
18. **Chaudhuri, A. and Behan, P.** (2000c), Fatigue and basal ganglia. Journal of Neurological Sciences 179: 34-42.
19. **Chesselet, M. and J. M. Delfs** (2003) Basal ganglia and movement disorders: an update. Vol. 19, no. 10, October 1996, Pages 417-422.
20. **Clark, D., Boutros, N., & Mendez, M**. (2005). *The Brain and Behavior.* Cambridge University Press.
21. **Churchland, M.M., B.M. Yu, S.I. Ryu, G. Santhanam, and K.V. Shenoy** (2006) Neural Variability in premotor cortex provides a signature of motor preparation. *Journal of Neuroscience*, **26**, 3697-3712.
22. **Cohen, J.D., T.S. Braver, and J.W. Brown** (2002) Computational perspectives on dopamine function in prefrontal cortex. *Current Opinion in Neurobiology*, **12**, 223-229.
23. **Contreras-Vidal and G. E. Stelmach (1996).** Effects of Parkinsonism on motor control. *Life Sciences*, *58*, 165-176.

24. **Crammond, D.J. and J.F. Kalaska** (1989) Neuronal activity in primate parietal cortex area 5 varies with intended movement direction during an instructed-delay period. *Experimental Brain Research*, **76**, 458-462.
25. **Cunnington, R., R. Iansek, J.L. Bradshaw, and J.G. Phillips** (1995) Movement-Related Potentials in Parkinsons-Disease Presence and Predictability of Temporal and Spatial Cues. *Brain*, **118**, 935-950.
26. **Czernecki V., B. Pillon, J. L. Houeto, J. B. Pochon, R. Levy and B. Dubois** (2002) Motivation, reward, and Parkinson's disease: influence of dopatherapy. *Neuropsychologia*, **40**, 2257-2267.
27. **Dayan, P. and L.F. Abbott** *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems*, MIT Press, Cambridge, 2001
28. **Daw, N.D. (2003),** Reinforcement Learning models of the dopamine system and their behavioral implications, Ph.D. thesis. Carnegie Mellon University, Pittsburgh.
29. **Daw, N.D. and Touretzky, D.S. (2000),** Behavior results suggest an average reward TD model of dopamine function, Neurocomputing 32:679-684 (2000)
30. **Daw, N.D., O'doherty, J.P., Seymour, B., Dayan, P. and Dolan R.J.** (2006), Cortical substrates for exploratory decisions in humans, Nature 441:876-879 (2006)
31. **Dean W. H. and G. D. Davis** (1958) Behavior changes following caudate lesions in rhesus monkeys, *Journal of Neurophysiology*, **22**, 165-187.
32. **Dorigo, M. and M. Colombetti** (1996) The robot shaping approach to autonomous robotics. *IEEE Colloquium on Self learning robots*, **12**, 1-4.
33. **Doya, K.** (2002) Metalearning and Neuromodulation. *Neural Networks*, vol. 15. no. 4, 495 – 506.
34. **Doya, K., K. Samejima, K. Katagiri, M. Kawato** (2002) Multiple model-based reinforcement learning. *Neural Computation*,**14**, 1347-1369.
35. **Doyon, J., Penhune, V., Ungerleider, L.G.** (2003). Distinct contribution of the corticostriatal and cortico-cerebellar systems to motor skill learning. *Neuropsychologia* **41**(3), 252–262.
36. **Engelborghs S, P. Marien, B. A. Pickut, S. Verstraeten and P. P. De Deyn** (2000). Loss of psychic self-activation after paramedian bithalamic infarction. *Stroke*, **31**, 1762-1765.
37. **Eslinger P. J. and A. R. Damasio** (1985) Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology*, **35**, 1731-1741.
38. **Frank, M.J.** (2005). Dynamic dopamine modulation in the basal ganglia: A neurocomputational account of cognitive deficits in medicated and non-medicated Parkinsonism. *Journal of Cognitive Neuroscience, 17,* 51-72.
39. **Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A**. (1994) The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med*; 121: 953–9.
40. **Fuster J. M.** (1997) The prefrontal cortex, Raven Press, New York.
41. **Gabrieli, J. D. E., R. A. Poldrack and J. E. Desmond** (1995) The role of left prefrontal cortex in language and memory. *Advances in Neurology*, **66**, 21-34.
42. **Gangadhar, G., Joseph, D., Chakravarthy, V.S.** (2007), "An oscillatory neuromotor model of handwriting generation," International Journal of Document Analysis and Recognition, Vol. 10, No. 2, November 2007.
43. **Gangadhar, G., Joseph, D., Chakravarthy, V.S.,** Understanding Parkinsonian Handwriting using a computational model of basal ganglia, Neural Computation **20, 1–35** (2008).

44. **Georgiou, N., Iansek, R., Bradshaw, J.L., Phillips, J.G., Mattingley, J.B. (1993)**. An evaluation of the role of internal cues in the pathogenesis of Parkinsonian hypokinesia. Brain, 116, 1575-1587.
45. **Georgopoulos, A.P. and S. Grillner** (1989) Visuomotor coordination in reaching and locomotion. *Science*, **245**, 1209-1210.
46. **Gerfen, C.R. and C.J. Wilson**. *The basal ganglia*. pp. 371-468. *In* **L.W. Swanson, A. Bjorklund, and T. Hokfelt** (eds.) *Handbook of chemical neuroanatomy*, Elsevier, Amsterdam, 1996.
47. **Ghika-Schmid F. and J. Bogousslavsky** (2000) The acute behavioral syndrome of anterior thalamic infarction: a prospective study of 12 cases. *Annals of Neurology*, **48**, 220-227.
48. **Giladi, N., D. McMahon, S. Przedborski, E. Flaster, S. Guillory, V. Kostic, and S. Fahn** (1992) Motor blocks in Parkinson's disease. *Neurology*, **42**, 333-339.
49. **Goldman-Rakic P. S.** *Circuitry of primate prefrontal cortex and regulation of behaviour by representational memory.* pp. 373--417. *In* **Plum F and U. Mountcastle** (eds.) *Handbook of physiology*, The American Physiological Society, Washington, 1987.
50. Hikosaka, O., Nakahara, H., Rand, M.K., Sakai, K., Lu, X., Nakamura, K., Miyachi, S., Doya, K., 1999. Parallel neural networks for learning sequential procedures. *Trends in Neuroscience*, **22**, 464–471.
51. **Hollerbach, J.M.** (1981) An Oscillation Theory of Handwriting. *Biological Cybernetics*, **39**, 139-156.
52. **Houk, J. C., J. L. Davis, and D. G. Beiser.** *Models of Information Processing in the Basal Ganglia*. MIT Press, Cambridge, MA, 1995**.**
53. **Hurtado, J.M., C.M. Graym L.B. Tamas, and K.A. Sigvardt** (1999) Dynamics of tremor-related oscillations in the human globus Pallidus: A single case study. *Neurobiology*, **96**, 1674-1679.
54. **Iversen, S.D.** (1979) Behaviour after neostriatal lesions in animals. In: Divac I, Oberg RGB (eds) The neostriatum. Pergamon, Oxford, pp 195–210.
55. **Joel, D., Y. Niv, and E. Ruppin** (2002) Actor-critic models of the basal ganglia: new anatomical and computational perspectives. *Neural Networks*, **15**, 535-547.
56. **Kacelnik, A. and D. Brunner** (2002) Timing and Foraging: Gibbon's Scalar Expectancy Theory and Optimal Patch Exploration. *Learning and Motivation*, **33**, 177-195.
57. **Kakade and Dayan (2002).** Dopamine: Generalization and Bonuses, Neural Networks, Vol. 14, No. 4, pp. 549-559.
58. **Knight, R. T., M. F. Grabowecky and D. Scabini (1995),** Role of human prefrontal cortex in attention control, *Adv Neurol* 1995; **66**: 21–36.
59. **Kornhuber, H.H. and Deecke, L. (1990).** Readiness for movement – The Bereitschafts potential-Story. Current Contents Life Sciences.33, 22 (1990).
60. **Kubota, K. and I. Hamada** (1978) Visual tracking and neuron activity in the post-arcuate area in monkeys. *Journal of Physiology (Paris)*, **74**, 297-312.
61. **Kubota, K. and S. Funahashi** (1982) Direction-specific activities of dorsolateral prefrontal and motor cortex pyramidal tract neurons during visual tracking. *Journal of Neurophysiology*, **47**, 362-376.
62. **Lang, W., D. Cheyne, R. Kristeva, R. Beisteiner, G. Lindinger, and L. Deecke** (1991) Three-dimensional localization of SMA activity preceding voluntary movement. *Experimental Brain Research*, **87**, 688-695.
63. **Leblois, A., T. Boraud, W. Meissner, H. Bergman and D. Hansel** (2006) Competition between feedback loops underlies normal and pathological dynamics in the basal ganglia. *Journal of Neuroscience*, **26**, 3567–3583.
64. **Levy, R. and B. Dubois** (2005). Apathy and the Functional Anatomy of the Prefrontal Cortex--Basal Ganglia Circuits, *Cerebral Cortex*, **16**, 916-928.

65. **Magnin, M., A. Morel, and D. Jeanmonod** (2000) Single-unit analysis of the pallidum, thalamus and Subthalamic nucleus in parkinsonian patients. *Neuroscience*, **96**, 549-564.
66. **Malapani, C., Rakitin, B., Levy, R., Meck, W.H., Deweer, B., Dubois, B., Gibbon, J.** (1998) Coupled temporal memories in Parkinson's disease: a dopamine-related dysfunction. *J. Cogn. Neurosci.* 10, 316–331 (1998).
67. **Marsden, C.D.** (1982). The mysterious motor function of the basal ganglia: the Robert Wartenberg Lecture, Neurology, 32(5):514-39.
68. **Matell, M.S. and W.H. Meck** (2004) Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes *Cognitive Brain Research*, **21**, 139-170.
69. **Mink, J.W.** (1996) The basal ganglia: focused selection and inhibition of competing motor programs. *Progress in Neurobiology*, **50**, 381-425.
70. **Mirenowicz, J. and W. Schultz** (1994) Importance of unpredictability for reward responses in primate dopamine neurons. *Journal of Neurophysiology*, **72**, 1024-1027.
71. **Montague, P.R. and G. Berns** (2002) Neural Economics and the Biological Substrates of Valuation. *Neuron*, **36**, 265-284
72. **Montague, P.R., P. Dayan, and T.J. Sejnowski** (1996) A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *Journal of Neuroscience*, **16**, 1936-1947.
73. **Montague, P.R., P. Dayan, C. Person, and T.J. Sejnowski** (1995) Bee foraging in uncertain environments using predictive Hebbian learning. *Nature*, **377**, 725-728.
74. **Montague, P.R., Hyman, S.E., and Cohen, J.D. (2004),** Computational Roles for Dopamine in Behavioral Control, Nature 431:760-767.
75. **Nini, A., A. Feingold, H. Slovin, and H. Bergman** (1995) Neurons in the globus Pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of Parkinsonism, *Journal of Neurophysiology*, **74**, 1800-1805.
76. **Obeso, J.A., M. C. Rodriguez-Oroz, F. J. Blesa and J. Guridi** (2006). The globus pallidus pars externa and Parkinson's disease. Ready for prime time? *Experimental Neurology*, **202**, 1–7.
77. **Oorschot D.E., Tunstall, M.J. and Wickens, J.R.** (2002), Local connectivity between striatal spiny projection neurons: A re-evaluation. *In* **L. Nicholson, and R. Faull** (eds.) *Basal Ganglia VII*, Plenum Press, New York, 2002.
78. **O'Reilly, R.C. & Frank, M.J.** (2006). Making working memory work: A computational model of learning in the frontal cortex and basal ganglia. *Neural Computation, 18,* 283-328.
79. **Packard, M. G., Hirsh, R., & White, N. M.** (1989). Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: Evidence for multiple memory systems. Journal *of Neuroscience, 9,* 1465–1472.
80. **Packard, M. G., and McGaugh, J.L.** (1996), Inactivation of Hippocampus or Caudate Nucleus with Lidocaine Differentially Affects Expression of Place and Response Learning, *Neurobiology of Learning and Memory*, **65,** 65–72 (1996)
81. **Packard M.G., and Knowlton B.J.** (2002) Learning and memory functions of the basal ganglia. *Annu Rev Neurosci* 25:563–593.
82. **Plenz, D. and Kitai, S.T.** (1999) A basal ganglia pacemaker formed by the Subthalamic nucleus and external globus Pallidus. *Nature*, **400**, 677-682.
83. **Prescott, T.J., K. Gurney, F. Montes-Gonzalez, M. Humphries, and P. Redgrave** *The robot basal ganglia: Action selection by an embedded model of the basal ganglia*. pp. 349-356. *In* **L. Nicholson, and R. Faull** (eds.) *Basal Ganglia VII*, Plenum Press, New York, 2002.

84. **Raz. A., E. Vaadia, and H. Bergman** (2000) Firing patterns of spontaneous discharge of Pallidal neurons in the model of Parkinsonism. *Journal of Neuroscience*, **20**, 8559-8571.
85. **Redgrave, P. T.J. Prescott, and K. Gurney** (1999*a*) Is the short-latency dopamine response too short to signal reward error? *Trends in Neurosciences*, **22**, 146-151.
86. **Redgrave, P. T.J. Prescott, and K. Gurney** (1999*b*) The basal ganglia: a vertebrate solution to the selection problem? *Neuroscience*, **89**, 1009-1023
87. **Russell, V.A. R. Allim, M.C. Lamm, and J.J. Taljaard** (1992) Regional distribution of monoamines and dopamine D1- and D2-receptors in the striatum of the rat. *Neurochemical Research*, **17**, 387-395.
88. **Sacco P, P. A. J. Hope, G. W. Thickbroom M. L. Byrnes and F. L. Mastaglia** (1999). Corticomotor excitability and perception of effort during sustained exercise in the chronic fatigue syndrome. *Clinical Neurophysiology*, **110**, 1883–91.
89. **Scheiner, R., S. Pluckhahn, B. Oney, W. Blenau, and J. Erber** (2002) Behavioral pharmacology of octopamine, tyramine, and dopamine in honey bees. *Neurology*, **42**, 333.
90. **Schultz, W.** (1998) Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, **80**, 1-27.
91. **Schultz, W., P. Dayan, and P.R. Montague** (1997) A neural substrate of prediction and reward. *Science*, **275**, 1593-1599.
92. **Servan-Schreiber, D., Printz, H. & Cohen J. D**. (1990), A network model of catecholamine effects: gain, signal-to-noise ratio and behavior. *Science* **249,** 892–895.
93. **Smith, Y., Bevan, M. D., Shink, E. and Bolam, J. P.** (1998), Microcircuitry of the direct and indirect pathways of the basal ganglia. *Neuroscience* 86, 353-387 (1998).
94. **Squire, L. R. and Zola, S. M.,** Structure and function of declarative and nondeclarative memory systems. Proc. Natl. Acad. Sci. USA, 1996, 93, 13515–13522.
95. **Sridharan, D., P.S. Prashanth, and V.S. Chakravarthy** (2006), The role of the basal ganglia in exploration in a neural model based on reinforcement learning. *International Journal of Neural Systems*, **16**, 111-124.
96. **Starr A, A. Scalise, R. Gordon, H. J. Michalewski, M. D. Caramia** (2000). Motor cortex excitability in chronic fatigue syndrome. *Clinical Neurophysiology*, **111**, 2025–2031.
97. **Stout, J. C. and S. A. Johnson** (2005) Cognitive impairment and dementia in basal ganglia disorders. *Current Neurology and Neuroscience reports*, **5**, 355 – 363.
98. **Stuss D. T., R. Van Reekum and K. J. Murphy.** *Differentiation of states and causes of apathy* pp. 340-363. *In* **J. C. Borod** (ed.) *The Neuropsychology of emotion*, Oxford University Press, Oxford.
99. **Suri, R.E. and W. Schultz** (1999) A neural network model with dopamine-like reinforcement signal that learns a spatial delayed response task. *Neuroscience*, **91**, 871-890.
100. **Sutton, R.S. and A.G. Barto** *Reinforcement Learning: An Introduction*, MIT Press, Cambridge, MA, 1998.
101. **Sutton, R.S. and A.G. Barto**. *Time-derivative models of Pavlovian reinforcement. In* **M. Gabriel and J. Moore** (eds.) *Learning and Computational Neuroscience*, MIT Press, Cambridge, MA, 1990.
102. **Tanji, J.** (1994) The supplementary motor area in the cerebral cortex. *Neuroscience Research*, **19**, 251-268.
103. **Terman, D., J.E. Rubin, A.C. Yew, and C.J. Wilson** (2002) Activity patterns in a model for the Subthalamopallidal network of the basal ganglia. *Journal of Neuroscience*, **22**, 2963-2976.

104. **Thut G, W. Schultz, U. Roelcke, M. Nienhusmeier, J. Missimer, R. P. Maguire and K. L. Leenders** (1997) Activation of the human brain by monetary reward. *Neuroreport*, **8**, 1225--1228.
105. **Tremblay L and W. Schultz** (1999) Relative reward preference in primate orbitofrontal cortex. *Nature*, **398**, 704-708.
106. **Usher, M., J.D. Cohen, D. Servan-Schreiber, J. Rajkowski, and G. Aston-Jones** (1999) The role of locus coeruleus in the regulation of cognitive performance. *Science*, **22**, 549-554.
107. **Wickens, J.** (1997), Basal ganglia: structure and computations, *Network: Computation in Neural Systems*, vol. **8**, no. 4, R77-R109.
108. **Wise, P.M.** (1982) Norepinephrine and dopamine activity in microdissected brain areas of the middle-aged and young rat on Proestrus. *Biology of Reproduction*, **27**, 562-574.
109. **Worgotter, F. and B. Porr** (2005) Temporal Sequence Learning, prediction, and Control: A review of different models and their relation to biological mechanisms. *Neural Computation*, **17**, 245-319.
110. **Duan, Y., Liu, Q., and Xu, X.H.** (2007). Application of reinforcement learning in robot soccer, Engineering Applications of Artificial Intelligence, Vol. 20, No. 7, pp. 936-950.