Basal ganglia: Structure and computations

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TOPICAL REVIEW

Basal ganglia: structure and computations

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Abstract. Until recently the basal ganglia of the mammalian brain have attracted little attention from theoretical neurobiologists. Traditional views of the functioning of the basal ganglia are based on their biomedical importance in disorders such as Parkinson's disease. Their contribution to normal brain functions has remained poorly understood. Experimental investigations over the past few decades have produced a wealth of detailed information about the structure of the basal ganglia and the physiological properties of their component neurones. It has become evident that the basal ganglia play a role in the selection and performance of learnt behaviours, and also in the effects of reinforcement on acquisition and maintenance of new behaviours. At present it is difficult to link the symptoms of basal ganglia disorders to these basic facts, in part because very few theoretical models attempt to incorporate the information that is now available. Computational modelling can help to advance theoretical understanding in this area by establishing explicit links between different levels of organization: from the effects of neurotransmitters such as dopamine on synaptic plasticity, through the dynamic interactions within subpopulations of neurons, to system-level interactions between the basal ganglia and cerebral cortex. The aim of this review is to outline existing knowledge of the basal ganglia in relation to previous computer modelling work, and to suggest ways of making use of the new experimental findings in the next generation of models.

Contents

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1. Introduction

The mammalian basal ganglia have received comparatively little attention from theoretical neurobiologists. In part this is because the overall functions of the basal ganglia are poorly understood. Traditional concepts of basal ganglia function are derived from clinical observations in humans. It has been known since the turn of the century that pathological changes in the basal ganglia and related structures are associated with disorders of movement. A number of distinct movement disorders have been recognized as due to diseases affecting the basal ganglia or closely related structures [130, 257], of which Parkinson's disease and Huntington's disease are classical examples. Although the pathological changes in these diseases are well documented the links between the motor symptoms and the disorders of the underlying mechanisms remain unclear [144].

The work of basal ganglia researchers over the past few decades has produced a wealth of new knowledge about the anatomy of the interconnections among neurochemically defined neurones in the basal ganglia. A number of informal theories have been inspired by consideration of the anatomical organization of the basal ganglia [22, 79, 151, 152, 154, 160, 161, 231, 234, 235]. Although experimental scientists working in these areas increasingly recognize computer simulation as a useful tool for dealing with such complex interactions [78], there have been very few attempts to make computer simulation models that accurately represent what is currently known about the anatomical structure of the basal ganglia. The aim of this review is to outline current knowledge of basal ganglia structure and function, using evidence from primary sources, and emphasizing those aspects most relevant to the construction of a new generation of network models.

1.1. Major structures of the basal ganglia

Most of the experimental findings referred to in this review are from studies conducted on the rat brain. The major subdivisions of the basal ganglia of the rat are illustrated in figure 1(A). The striatum is the input structure of the basal ganglia, receiving excitatory inputs from the entire cerebral cortex, from dopamine neurones with cell bodies located in the substantia nigra, and from the thalamus. The striatum sends projections to the substantia nigra, entopeduncular nucleus and globus pallidus. Neurones in the substantia nigra and entopeduncular nucleus in turn project to the basal ganglia receiving area of the thalamus, which is reciprocally connected with frontal areas of the cerebral cortex. The subthalamic nucleus forms a circuit involving the globus pallidus, substantia nigra and entopeduncular nucleus. The number of neurones in each structure is shown on the figure, as determined by a recent stereological investigation [173].

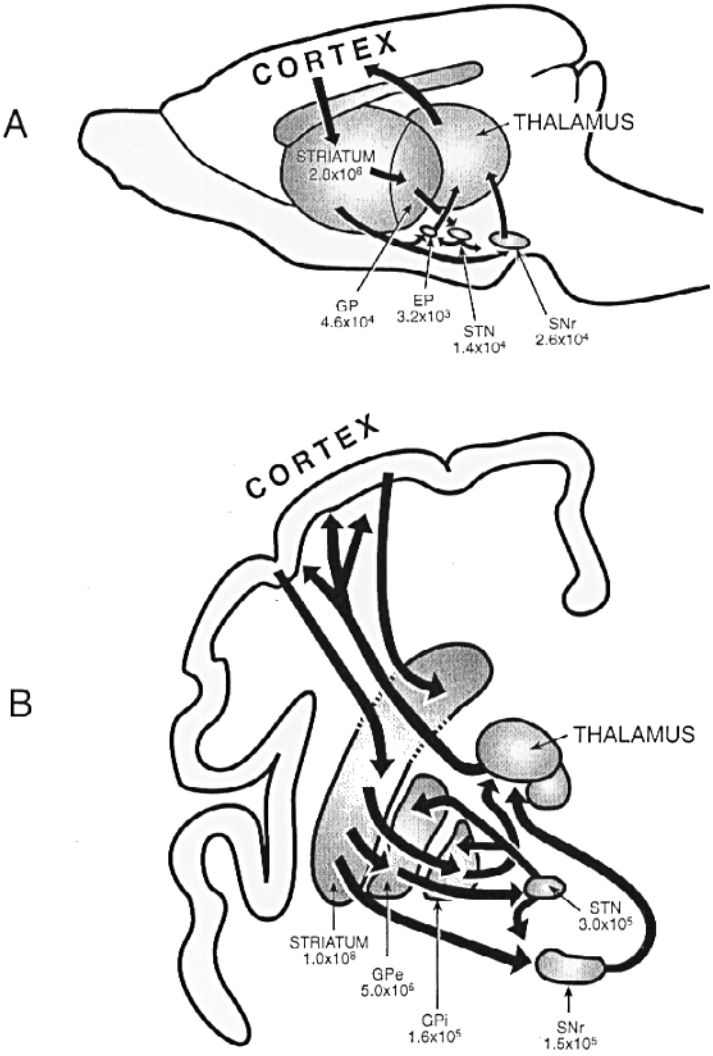

Figure 1. Schematic diagram of the major structures of the basal ganglia and their interconnections. (A) Rat brain, sagittal section. Adapted from Oorschot [173], with permission of the author. (B) Human brain, coronal section. Abbreviations: GP, globus pallidus; GPi, internal segment of globus pallidus; GPe, external segment of globus pallidus; EP, entopeduncular nucleus; STN, subthalamic nucleus; SNr substantia nigra, pars reticulata. Numbers indicate the total number of neurones within each structure.

The similarities between the neurones of the rat and the human basal ganglia far outweigh the differences, as far as they are currently known. However, there are obvious differences in the numbers of neurones and in the way neurones are grouped or subdivided into different nuclei. Estimates of the total numbers of neurones in each of the major subdivisions of the human basal ganglia are shown in figure 1(B) [127, 221]. Note that in humans the striatum is subdivided into the caudate nucleus and putamen by the internal capsule, and the homologue of the rat entopeduncular nucleus (EP) is the internal segment of the globus pallidus (GPi).

1.2. Disorders and lesions of the basal ganglia: implications for functions

Conspicuous abnormalities of motor function occur in association with many diseases of the basal ganglia. In the first few decades of this century a syndrome of muscular rigidity, distorted posture and abnormal movements was found to be associated with pathological changes in various parts of the basal ganglia [93, 257, 258, 259]. The abnormal movements included involuntarily writhing movements of the face, tongue and extremities or flickering movements tending to dance from one muscle group to another: a symptom known as chorea. The correlation of unwanted movements with degeneration of the basal ganglia led to the view that their normal function is to inhibit unwanted movements [130].

More recent neuropathological findings in Huntington's disease suggest that this simplified view is partially correct. Huntington's disease is a genetically determined degenerative disorder. Unwanted movements such as chorea are a conspicuous feature of the early stages of the disease process, and are associated with a decrease in the number of neurones in the striatum [225]. A number of informal models have attempted to explain the relationship between loss of striatal neurones and the symptom of chorea [2]. In the early states of Huntington's disease, when chorea is most evident, the degenerative changes are most marked in the pathways connecting the striatum to the external segment of the globus pallidus (GPe) [1]. The pathway from the GPe to the subthalamic nucleus (STN) is the first of three inhibitory links in a chain between the output of striatal neurones and motor areas in the thalamus (see figure 2(A)). Arguably, the net effect of this odd number of inhibitory synapses in series could be inhibition of movements, and loss of such inhibition could release unwanted movements that are normally kept suppressed.

In Parkinson's disease there is also neuronal degeneration, but it is the dopaminergic afferents to the striatum from the substantia nigra that are most predominantly affected. The motor symptoms in Parkinson's disease include tremor, muscular rigidity, and difficulty initiating movements (akinesia). In experimental models, some of these symptoms are associated with increased activity in the GPi [55], and may be reduced by a surgical lesion of the STN [23]. Again, by counting up the number of inhibitory synapses in series, one can argue that in Parkinson's disease there is a net reduction of output from the basal ganglia and thus an overall increase in movement inhibition.

These informal models are familiar to medical students everywhere, and appear to provide a logical explanation for the spectrum of movement disorders seen in basal ganglia diseases. However, it is important to recognize the different levels of organization involved, and not to confuse inhibition of a neuron, or group of neurones, with inhibition of a movement. Neural activity which is inhibitory for one class of movements may be facilitatory for another class. Also, strictly speaking one cannot say that one nucleus inhibits another nucleus, because the output from a nucleus is usually a temporospatial pattern of activity in which some neurones may be increasing their activity when others are decreasing. However, consistent with such models treatment of Parkinson's disease by stereotaxic neurosurgery is remarkably successful. In particular, small lesions in the globus pallidus and motor thalamus reduce tremor and rigidity without making other symptoms worse [145].

Cognitive functions of the basal ganglia have not been widely recognized, in part because the conspicuous motor disorders overshadow less obvious cognitive dysfunctions. Although psychiatric disorders do occur in Huntington's disease, it is possible that they are related to effects of the disease on other parts of the brain, or to the enormous psychological burden imposed by knowing what lies ahead. On the other hand, a number of neuropsychiatric illnesses have been associated with basal ganglia dysfunction. Included among these are schizophrenia [64], obsessive–compulsive disorder [194], attention-deficit hyperactivity

disorder [87], and a syndrome described as psychic akinesia [128]. The most common symptom after lesions of the caudate nucleus is a syndrome of apathy with loss of initiative and spontaneous thought and emotional responses [25]. It is increasingly apparent that the basal ganglia are involved in cognitive functions as well as in the control of movement.

Learning deficits affecting the acquisition of procedural knowledge are also recognized in human subjects with basal ganglia disorders [36, 131, 133, 217, 219]. The deficits are subtle but imply a role for the basal ganglia in the acquisition of certain forms of learning. In animals, experimental lesions of the basal ganglia produce marked deficits in particular types of learning, above and beyond what could be accounted for by impairment in motor performance [38, 132, 171, 172, 220, 261]. Based on such data several authors have made specific proposals about learning functions of the basal ganglia [151, 160, 161, 231]

1.3. Issues for computational models of the basal ganglia

Although pathological changes in a number of basal ganglia disorders are well documented, the links between the symptoms and the underlying mechanisms are far from clear. In order to establish such linkages it will be necessary to integrate several different levels of organization: synapses, networks, systems of networks and motor activity. An explanation of symptoms in such terms would be helpful, and computer simulation can, in principle, help to establish such links.

It would also be helpful to understand the operations that are normally performed by the basal ganglia. For example, what do basal ganglia circuits contribute to cortical functions? The macroscopic organization of the basal ganglia provides fuel for speculation. An obvious feature is the partially closed loop circuit that is formed by tracing the connections of the basal ganglia, from cortex through striatopallidal complex to thalamus and back to cortex. The projection from the cerebral cortex is massive and originates from all major areas [149]. This seems to give the striatum a unique vantage point, for no other brain structure is in a position to monitor activity in all regions of the cerebral cortex by direct connections. What is the advantage of this? These connections all terminate on dendritic spines: structures often associated with learning and memory mechanisms. Is the striatum part of a cortical–subcortical circuit for particular types of learning and memory?

The convergence in the striatum of inputs from the midbrain dopamine neurones with inputs from the cerebral cortex is another important clue to the function of the basal ganglia. The dopamine neurones appear to fire in response to unexpected reward or predictors of reward [158, 159]. The striatum may be a site at which reward signals are integrated with information about cortical activity patterns representing motor or sensory antecedents of reward. The operations performed in relation to this information have important implications for understanding reward-related learning mechanisms. However, even though this aspect of basal ganglia function is now well recognized, it is unclear how these operations are connected with the symptoms of abnormal dopamine function in disorders such as Parkinson's disease and schizophrenia.

The following sections review current knowledge of basal ganglia structure and physiology, focussing on issues relevant to current neural models. The probable facts are emphasized in order to bias models towards actual anatomy and physiology rather than functions attributed on the basis of evidence from experimental lesions. Computer simulations that have already appeared are reviewed. These are clearly at an embryonic stage and have scarcely begun to take on board current knowledge of basal ganglia anatomy and physiology. The review concludes with some suggestions for the next generation of neural models of the basal ganglia.

2. The striatum

The striatum is the largest component of the basal ganglia. It is also the primary input region, and receives excitatory inputs from all areas of the cerebral cortex, from intralaminar nuclei in the thalamus, and from dopamine projections from the midbrain. The forebrain glutamate and midbrain dopamine inputs converge within the striatum and terminate close to one another on the spiny projection neurones, the principal output neurones of the striatum. The principal output neurones effectively form a single layer of spiny neurones between the cortical inputs and the striatal outputs, and they are also the site at which dopaminergic inputs are integrated with cortical inputs. This implies that the functional properties of the corticostriatal synapses, the response properties of spiny projection neurones and the effects of dopamine on these properties are key determinants of the signal processing operations performed in the striatum.

2.1. Spiny projection neurones

The great majority of striatal neurones are projection neurones with a spine-free cell body and a densely spiny dendritic tree. In the rat, these projection cells account for a remarkable 97% of the neurones of the striatum [174]. The shapes of the dendritic and axonal arborizations, particularly the overlap of the axons of one neuron with the dendrites of its neighbours, indicate what synaptic connections may be formed between projection neurones, and are worth considering in detail. The dendritic tree is formed by several primary dendrites which radiate from the cell body and divide to form secondary and tertiary dendrites extending within a spherical or ovoid volume of about 250–500 μm in diameter. A main axon originates close to the cell body and projects to target structures and also gives rise to local axon collaterals which divide repeatedly to form an extensive network which overlaps extensively with the dendritic tree [253].

The projection neurones are GABAergic. The majority of spiny projection neurones stain positively with moderate intensity for glutamate decarboxylase (GAD), the synthesizing enzyme for GABA [29, 113, 169]. GAD-positive boutons form synapses with the cell body and dendrites of neurones identified as projection neurones by retrograde labelling from the substantia nigra [16]. Immunohistochemical staining for GABA has identified numerous synapses between GABA-positive boutons and similarly staining dendrites [177]. Thus, almost all of the neurones are GABAergic and probably inhibitory to other neurones within the striatum, as well as to target neurones in projection areas. This is a striking feature of the striatum.

The extensive collateral arborizations of the GABAergic spiny projection neurones have led several authors to propose that inhibitory interactions between spiny projection neurones within the volume reached by their dendrites and axon collaterals may be a central organizing principle in the striatum [79, 176, 191]. These proposals have formed the basis for several computer models [120, 237, 238, 241]. However, the assumption that inhibitory interactions occur among spiny projection neurones is based on anatomical evidence. The physiological evidence for and against such interactions is therefore given close scrutiny in the following discussion.

Initial studies of the responses of striatal cells to cortical stimulation appeared to be consistent with the idea of lateral inhibitory interactions. Striatal neurones respond to cortical stimulation in a characteristic sequence of an initial brief excitation followed by a longer-lasting (100–350 ms) period of inhibition. Intracellular studies confirmed that the initial excitation was due to an excitatory postsynaptic potential (EPSP), and that this was

followed by a period of relative hyperpolarization, presumed to be an inhibitory postsynaptic potential (IPSP). This EPSP–IPSP sequence appeared to be consistent with the idea of a population of spiny projection neurones that was first excited by a wave of activity in corticostriatal afferents, and subsequently inhibited, presumably by feedback from other excited spiny projection neurones.

Subsequent experiments have shown that these first appearances were misleading. The long-lasting 'IPSP' was not reduced by locally applied GABA antagonists [24] and was not observed in vitro [134, 135]. Instead, Wilson *et al* [251] showed that this so-called inhibition was not due to a hyperpolarizing or shunting IPSP at all. Rather, it was a period of disfacilitation due to a reduction in cortical excitatory input following the stimulus, presumably brought about by interactions outside the striatum.

Although it is now clear that the long-lasting inhibition is not due to feedback inhibition among spiny projections neurones a fast IPSP still remains even in striatal slices [134, 135]. This fast IPSP is probably due to feedforward interneurones [109]. To date it has not been shown that fast duration IPSPs can be induced in spiny projection neurones by other spiny projection neurones. Inhibition of a striatal neurone by its own collaterals, however, has been demonstrated by Park *et al* [176]. Action potentials evoked in the recorded neurone by a depolarizing current pulse reduced the amplitude of EPSPs evoked from stimulation of the substantia nigra. This effect was blocked by GABA antagonists. These results suggest that spiny projection neurones may be inhibited by their own collaterals. It is particularly noteworthy that EPSPs evoked by cortical stimulation were not inhibited in the same way. This appears to be because the EPSPs evoked by substantia nigra stimulation (probably produced by collaterals of corticofugal axons passing in the nearby cerebral peduncle) were electronically more distant from the soma than those evoked by cortical stimulation.

One would expect that the spiny projection neurones would be likely to exert a similar effect on their neighbours, there being no obvious way for the axons of a given neurone to distinguish its own dendrites from those of other neurones. In support of this, Katayama *et al* [99] showed that antidromic activation of striatal neurones by stimulation in the entopeduncular nucleus produced short latency suppression of firing in other nearby spontaneously firing neurones. The short latency suppression was blocked by GABA antagonists, but was not reduced by removal of the cerebral cortex, suggesting that it might reflect lateral inhibitory interactions between spiny projection neurones. However, in the only direct study to date, Jaeger *et al* [92] made intracellular records from pairs of spiny projection neurones in slices. They found no evidence for inhibition of one spiny neurone by another, neither in the form of IPSPs, suppression of firing evoked by current injection, nor reduction of cortically-evoked EPSPs.

In summary, the most that can be said at present is that inhibitory interactions among spiny projection neurones, if they exist at all, are weak and limited to electronically distant inputs. Strong inhibitory interactions do not occur under the conditions that normally exist in slices, or in anaesthetized animals, in which the studies referred to above have been performed. On the other hand, evidence supporting the view of the striatum as a lateral inhibitory network has been obtained in co-cultures of cortex and striatum [184]. Furthermore, the negative findings reported so far do not rule out other possibilities. Strong interactions might appear in the presence (or absence) of neuromodulators such as dopamine or acetylcholine. A hint of evidence supports this suggestion [109]: IPSPs can be evoked by antidromic stimulation when synaptic transmission is enhanced by 4-aminopyridine, a substance that prolongs action potential duration. With advances in techniques for making dual intracellular records from striatal cells it may become feasible to measure inhibitory interactions under a range of different conditions, and test these possibilities.

2.2. Striatal interneurones

In addition to the spiny projection neurones the striatum contains several classes of interneurones, which may be distinguished by their physiological, anatomical and histochemical characteristics [103]. Although interneurones make up a very small percentage of the total number of neurones in the striatum, they produce diverse neurotransmitters in relatively high concentrations. It seems likely that the interneurones play a particularly important role in striatal function, imposing local variations in levels of modulatory neurotransmitters such as acetylcholine, on an otherwise uniform network of spiny projection neurones.

The cholinergic interneurones are of particular interest from a pharmacological and clinical perspective, because anticholinergic drugs are useful in the treatment of Parkinson's disease, or to relieve side-effects of dopamine antagonist drugs. The cholinergic interneurones have large cell bodies and long, aspiny and infrequently branching dendrites. They give rise to a dense axonal plexus, the boutons of which form predominantly symmetrical synaptic specializations [28, 216]. The functional properties of large aspiny cells (which can be presumed to be cholinergic) have been studied in vitro. In comparison to the spiny projection neurones they have more depolarized resting membrane potentials and lower thresholds [101]. Cholinergic interneurones themselves receive synaptic input from many different types of axon involving a range of different neurotransmitters. They receive direct synaptic input from dopaminergic axons [121]. They also receive glutamatergic inputs from thalamostriatal afferents. Corticostriatal afferents form synapses on distal dendrites, but these contacts are infrequent [60] and not always observed [129, 150]. The spiny projection neurones are the major postsynaptic targets [91] of cholinergic interneurones.

The GABAergic interneurones stain very intensely for GABA, and can also be identified by the presence of an intracellular calcium binding protein, parvalbumin [50, 109]. These are probably feedforward interneurones, and are presumably responsible for the fast IPSP that follows orthodromic stimulation. They account for a very small percentage of the neurones of the striatum, but appear to have strong effects, perhaps because they have low thresholds and may fire repetitively in response to excitatory input.

2.3. Firing patterns of striatal neurones

The firing patterns of striatal neurones in animals that are awake gives some idea of the contribution of striatal neurones to behaviour. In animals that are awake the majority of striatal neurones are quiescent, firing at zero or few impulses per second most of the time [5, 52, 53, 54, 105, 106, 108, 201, 202]. This relative silence is interrupted by episodes during which action potential firing frequency is increased to moderate levels. Such episodes may last between 100 ms and a few seconds. During an episode the neurones fire several action potentials in an irregular cluster [254]. When recorded in the striatum of an awake behaving animal, the clusters of firing occur in association with a particular aspect of the task being performed, such as a movement on the part of the animal [5, 52, 53, 136, 137, 230].

The phasic, movement-related neurones include a subset of neurones that are selective for movements in a particular direction. In about half of these movement-related neurones, the loading conditions and underlying pattern of muscular activity do not appear to influence the discharge rate [53]. Thus, there is a significant proportion of striatal neurones encoding direction of movement, rather than specific details of muscle activity. About 20% of the movement-related cells are selectively related to preparation for performance of active movements but not for the same movements performed passively. These may fire several

hundred milliseconds in advance of a movement and thus are thought to play a role in preparation, timing or initiation of movement [5, 105, 106, 201].

In many striatal neurones the nature of the association of neural activity with sensory cues and movement depends on the behavioural context [3, 168]. For example, neurones may respond to environmental events when they are cues in a visual discrimination task, but not when the same events occur in a different context outside the task [190]. Such neurones are reported to be relatively rare in the putamen, where neurones unconditionally associated with movements are more common [189]. Many neurones have been observed that do not discharge during spontaneously initiated movements, but do discharge when a learned movement is triggered by a sensory stimulus [105, 106, 108]. Thus, the firing activity of striatal output neurones is often highly selective, but is seldom unconditionally associated with particular sensory or motor events. Rather, it appears to reflect acquired, conditional associations between sensory stimuli and motor responses.

In addition to the striatal neurones that fire during extracellular studies of single unit activity, intracellular studies reveal that a large fraction of striatal neurones is silent prior to impalement and may remain silent for recording periods lasting several minutes or even hours. These silent spiny neurones are morphologically indistinguishable from spontaneously firing neurones, and are capable of firing in response to applied current pulses and evoked EPSPs [254]. Probably the great majority of striatal neurones are silent, becoming active only in relation to specific stimuli or responses. The factors which regulate the transition from quiescence to firing activity are thus of central importance in understanding the functioning of the striatum, and are likely to involve regulation of membrane conductances that are active in the subthreshold range of membrane potentials [248, 255], as well as excitatory inputs from the cerebral cortex (see subsection 2.4).

A second, but less common, type of neural activity which is tonic rather than episodic has also been described in the striatum [106, 108]. These tonically firing neurones do not project to the globus pallidus [107] and are probably the cholinergic interneurones referred to above [252].

A third type of activity described in striatal single unit studies is a phasic burst that appears specifically prior to a sequence of movements, but not to the individual movements in the sequence. These neurones produce an episode of firing activity preceding the first movement of a sequence of repetitive movements but are almost inactive during succeeding movements [106]. Their identity has not been determined but it has been suggested that these might be the feedforward inhibitory interneurones performing some kind of blanking function prior to the onset of sequential firing activity [238].

The activity of the spiny projection neurones is determined in part by the regulatory effects of cholinergic and GABAergic interneurones, and possibly also feedback from other spiny projection neurones; However, the main excitatory drive is derived from the synaptic inputs they receive from the cortex, as considered in the following section.

2.4. Organization of corticostriatal afferents to the striatum

The cerebral cortex is a major source of excitatory input to the striatum. Cortical afferents to each striatum originate from all major cortical regions bilaterally, with an ipsilateral predominance [149]. This gives the striatum a unique vantage point from which to monitor the state of the entire cerebral cortex. Although it is not yet clear which aspects of cortical activity are being sampled for use by the striatum, the laminar origins of corticostriatal afferents suggest that there may be several corticostriatal processing systems superimposed, each of which is concerned with monitoring a different aspect of cortical activity.

The neurones that project from the cortex to the striatum are pyramidal neurones with cell bodies located in cortical laminae II–VI [69, 82, 94, 170, 192, 203, 260]. The proportion of corticostriatal neurones in each cortical lamina varies across cortical areas [13, 218, 245]. Several major cortical efferent projections have collateral branches to the striatum [249]. The major types (each with corticostriatal collateral projections) include: cortico-cortical neurones located in the superficial half of layer V and deep part of layer III; cortico-thalamic neurones projecting to the thalamus; and brainstem projecting cortical neurones located in layer V of sensorimotor areas. The latter innervate the striatum via collateral branches arising in the internal capsule [63] and are distinctive in being entirely of ipsilateral cortical origin [244].

The transformations that occur in the corticostriatal projection present an intriguing problem for theorists. The corticostriatal axons produce extended arborizations within a relatively large volume of the striatum [49, 58]. Presumed synaptic contacts are sparse and when their distribution is compared with the dendritic tree of spiny projection neurones it is clear that a single corticostriatal neurone probably makes not more than three or four synaptic contacts with any given spiny projection neurone [249]. Individual striatal projection neurones receive only few synapses from any given cortical area [208]. In general, individual corticostriatal afferents appear to make synapses over a significant fraction of the whole striatum, but they make only few synapses with any given striatal neurone [79]. The neocortical afferents to the striatum form most of their contacts with the spines of spiny projection neurones, where they make asymmetric synapses [208]. The neurotransmitter in this pathway is probably glutamate [147, 148]. The effects of individual corticostriatal synapses are moderately small [163], such that several tens of active inputs may be required to depolarize the postsynaptic neurone to its threshold membrane potential.

Despite the presumably small contribution of individual corticostriatal inputs to firing of postsynaptic striatal neurones, the corticostriatal inputs are an important, if not the major determinant of the episodic firing pattern of spiny projection neurones. Removal of the cortex reduces the frequency and intensity of the episodes of firing of striatal neurones [4, 229]. The low rates of spontaneous activity in corticostriatal neurones [21] combined with the relatively many unitary postsynaptic potentials required to fire the striatal projection neurones suggests that the active ones must be receiving convergent inputs from many corticostriatal cells, or highly synchronized inputs from a smaller number of repetitively firing cells. The occurrence of temporally coincident activity in many axons that is necessary to fire striatal cells therefore implies coactivation or synchronization of corticostriatal cells distributed over a wide area of cerebral cortex.

Neither the exact number nor the density of corticostriatal neurones is known, and it is difficult to estimate the ratio of corticostriatal to striatal neurones. The projection of almost the entire cerebral cortex upon the striatum suggests there is extensive convergence of cortical inputs such that an individual spiny projection neurone samples from an extensive area of cortex. Anatomical and electrophysiological studies also indicate considerable convergence from some areas of cortex onto individual striatal cells [256] or restricted striatal areas [70], though this is not true for all areas [195].

While these transformations could be summarized as a mixture of convergence and divergence, the picture is complicated by the patchiness of terminations. The organization of the corticostriatal projection is complicated, and it is unclear how it should be approached. One possibility is to consider the projections of functionally related areas of cortex on to the striatum. For example, Künzle [122, 123, 124] suggested that cortical areas that were interconnected in the cortex converged in the striatum. On a local microscopic scale such a pattern of convergence exists, in which different selections of cortical inputs are combined

in different ways at different striatal sites. There appears to be a systematic remapping such that projections from different bodily regions (such as hand, mouth and foot areas) within a given somatosensory area remain segregated, while projections from different somatosensory areas, representing different sensory modalities for the same bodily parts, send projections that converge in the striatum [52, 141]. Thus, information from different parts of the body is kept separate (in a somatotopic framework), while there is convergence of information concerning different modalities, but the same bodily parts. Using functional imaging techniques it has also been shown that somatosensory stimulation of different limb and trunk regions produces a functional map of striatal activation that changes at different antero-posterior levels [35]. Thus, at different levels, different combinations of afferents associated with different body regions are brought into juxtaposition.

One of the difficulties of anatomical description in this area is the lack of concepts for describing mappings. Somatotopic mappings to which all other possibilities are compared are most meaningful in the context of transformations of the Cartesian plane, and have an obvious interpretation with respect to preservation of spatially patterned information. The patterns and transformations that are relevant to corticostriatal operations are far from obvious, however, and they do not obey simple geometrical laws.

2.5. Striatal dopamine: its role in reinforcement and synaptic plasticity

In addition to extensive glutamatergic afferents from the cortex, the striatum receives a dense dopaminergic innervation from the substantia nigra and ventral tegmental area. Although the striatum is only one among many areas of the brain which receive a dopaminergic input, it is the area with the highest levels of dopamine. Within the striatum, the dopaminergic axons form thin beaded branches and collaterals, which profusely branch to form a fine feltwork of terminal branches [58]. Dopaminergic synapses are made on the spiny projection neurones and also on cholinergic interneurones [121]. The striatum in general, and the spiny projection neurones in particular, are thus a site at which there is convergence of glutamatergic inputs from the cortex with dopaminergic inputs from the midbrain.

The specificity of connections implied by the intricate recombinations of corticostriatal inputs contrasts with the apparently more diffuse dopaminergic input from the midbrain. The synapses between dopaminergic afferents and spiny projection neurones are located very close to the glutamatergic synapses of the corticostriatal pathway, sometimes terminating on the base of the same dendritic spine that receives a corticostriatal synapse on its head [32, 73]. The dopamine synapses are thus very well placed to regulate the efficacy of the corticostriatal synapses.

Several pieces of evidence suggest that dopamine synapses may mediate some of the effects of behavioural reinforcement. Direct electrical stimulation of certain sites in the brain can produce conditioning effects similar to those produced by natural rewards. The most effective sites directly or indirectly activate the dopaminergic neurones in the midbrain [209]. Dopamine agonist drugs also produce positive reinforcement effects similar to those produced by natural rewards [85] whereas dopamine antagonist drugs attenuate the effects of reward [126]. The concentration of dopamine in the neostriatum is increased by rewards [84] and decreased by aversive stimuli [142]. This evidence implies a role for dopamine in reward mechanisms, but raises the issue of what dopamine might do at the cellular level. Behavioural responses which have been strengthened by reinforcement persist in the absence of continued reinforcement, during which time a decline in responding known as extinction occurs. If dopamine is a mediator of reinforcement then it should be able to produce long-lasting changes in synaptic strength, outlasting the period of exposure to dopamine.

Recent experiments have shown that striatal neurones develop new responses to task-related stimuli during learning and that these new responses persist for as long as performance is maintained [12]. The acquisition of both behavioural and neuronal responses studied in these experiments is dependent on the nigrostriatal dopamine system [11]. However, it should be noted that some researchers have found no evidence for such changes [37] and, secondly, that the changes that were observed took place in tonically active neurones which are presumably cholinergic interneurones rather than spiny projection neurones.

Activation of the dopamine afferents by direct electrical stimulation produces a mixture of effects on the activity of single neurones in the striatum. Both increases and decreases of responses to cortical stimulation are seen, some of which persist for at least several minutes [83]. Pharmacological manipulation of the dopamine system with drugs such as amphetamine results in long-lasting changes in the responses of cat striatal neurones to afferent inputs [198] and the converse, depleting dopamine, reduces the responses of striatal neurones to peripheral sensory stimulation [197].

Synaptic plasticity is a possible basis for the long-lasting changes in neuronal responses in the striatum reported above. Synaptic plasticity is a long-lasting change in the functional efficacy of synaptic connections that is induced by certain patterns of brain stimulation. It is widely used as an experimental model for learning and memory mechanisms of the brain [27]. Several authors have proposed that synaptic plasticity mechanisms underlie learning-related effects of dopamine in the striatum [22, 152, 155, 233, 240].

Experimental study of synaptic plasticity in the striatum has advanced rapidly over the past five years. Both long-term potentiation (LTP) and long-term depression (LTD) of synaptic responses have been described in the striatum. Long-term depression can be induced in the synapses connecting the cerebral cortex to the striatum by high-frequency stimulation of the cerebral cortex [39, 40, 41, 42, 139, 227]. It is a depolarization-dependent process that requires activation of voltage-sensitive calcium channels in the postsynaptic cell during the conditioning tetanus. In brain slices, activation of dopamine receptors is a requirement for LTD induction [39, 40]. The residual dopamine level in slices is apparently enough to support LTD. Thus, the tonic activity of the dopamine cells that would normally occur (rather than phasic reward-related activity [200]) would be sufficient to support LTD.

When dopamine is applied in brief pulses coinciding with the pre- and postsynaptic conjunction of activity the LTD is reversed and long-term potentiation (LTP) of responses is seen [239]. Thus, pulsatile application of dopamine reverses the long-term depression which normally follows high-frequency stimulation of the cortex. This long-lasting effect of dopamine is compatible with a rule for synaptic modification proposed by Miller [151] and Barto and Sutton [19], which will be considered in the following section.

2.6. Reinforcement learning and the striatum

The integration of synaptic plasticity into the overall functioning of the basal ganglia in reward-related learning requires a theoretical framework. There are several levels of analysis to consider. Firstly, synaptic plasticity phenomena as induced experimentally need to be detailed as explicit rules for synaptic modification. Secondly, these rules operate within local circuits involving corticostriatal and dopaminergic afferents, together with a network of spiny projection neurones. Thirdly, these circuits are, in turn, embedded within multiple layers of networks. These different levels of analysis are required to link synaptic plasticity in the corticostriatal pathway to reward-related learning functions of the basal ganglia as a whole.

In general, an organism attempting to learn on the basis of reward is likely to have

difficulty correctly attributing credit for an outcome to processes several steps removed from the output. This problem has become known as the credit assignment problem [157]. In the present context, the credit assignment problem is to select the appropriate synapses to modify, when the contribution of a given synapse to the outcome is buried in its past history or effects on relatively distant areas of the brain. In the context of such learning in artificial neural networks [118] it has been proposed that effective solutions can be found if certain conditions make a pathway 'eligible' to have its weight modified, and the pathway then remains eligible for some period of time after the conditions cease to hold. Barto *et al* [18] used such schemes to solve difficult learning control problems in what were termed associative search networks.

Reinforcement learning algorithms operating within associative search networks not only have enormous potential in machine learning, but also lead to new ways to formulate problems which traditionally belonged in the domain of behavioural learning theory [20, 104, 242]. Such networks combine two types of learning. They learn to solve a pattern recognition problem, by learning to respond to each particular stimulus with an output pattern. Secondly, they learn to produce the particular output pattern that is most appropriate, or optimal in the sense of bringing in the maximum reinforcement in the context of the stimulus [18, 19, 215]. Although they have limitations, such as being slow to converge when compared with other learning schemes, they are biologically plausible. In particular, the mechanisms required to implement these aspects of reinforcement learning algorithms appear to exist in the striatum [240].

The reinforcement learning rules proposed in the context of artificial neural networks have a formally identical counterpart in synaptic modification rules proposed on the basis of the logical form of instrumental conditioning, and localized to the striatum [152, 153, 233]. According to these rules, a conjunction of presynaptic and postsynaptic activity produces a 'state of readiness', which has a similar role to the eligibility trace referred to above. Activation of the reward or reinforcement signal produces strengthening of the synapses that are in a state of readiness. This three-factor rule for synaptic modification may be unique to the striatum, or reflect a feature of synaptic plasticity mechanisms that are also present in other brain areas receiving dopamine inputs [86].

A second important point to emerge from the theoretical study of reinforcement learning is the need for a mechanism to anticipate reinforcing events [17]. Such a device has been termed an 'adaptive critic' in computational models of learning [215]. The adaptive critic is a machine learning device that learns to anticipate reinforcing events. In conjunction with another adaptive element, the actor, which uses a simple algorithm to update its weights on the basis of recent activity and subsequent reinforcement, the actor-critic forms a powerful learning module [18, 19] that is able to deal with difficult learning control problems.

The phasic activity of dopamine neurones during successive stages of learning is strikingly similar to the behaviour of the adaptive critic [215]. Dopamine neurones have different modes of firing. Generally, they display tonic activity, firing regularly at low rates. However, in response to certain stimuli, they may fire a burst of action potentials lasting a few hundred milliseconds. The conclusion of a long series of studies in awake monkeys is that the most effective behavioural stimulus for burst firing of dopamine cells is an unpredicted appetitive stimulus such as food or drink [159]. During learning the dopamine neurones are activated in relation to such positively reinforcing stimuli [158]. As learning proceeds they begin to fire in response to predictors of reinforcement, such as lights signalling that a reward is available if a certain response is made [138].

In summary, there is some evidence that synaptic plasticity in the corticostriatal pathway underlies long-lasting changes in neural activity associated with behavioural learning. The

rules governing synaptic modification in the striatum are still far from clear, but there are similarities to the rules required for effective reinforcement learning in artificial neural networks. Furthermore, there is evidence to suggest that the dopamine afferents to the striatum may mediate some form of reward signal, activated by positive reinforcement. During learning, adaptive changes in the response of the dopamine neurones to behavioural reinforcement are compatible with the notion of an adaptive critic, a device which improves the performance of reinforcement leaning algorithms. Thus, there are promising indications of a fruitful cross-fertilization between the experimental study of synaptic plasticity and dopaminergic function in the striatum, and theoretical neural network approaches to difficult learning control problems.

The fast activity dynamics and long-lasting changes in synaptic efficacy described above are important factors controlling the output from the striatum. The following section considers how the output stages of the basal ganglia integrate and transform the output from the striatal projection neurones, and how it is eventually projected back to the cerebral cortex.

3. The pallidal–subthalamic complex: output stage of the basal ganglia

Most of the output from the striatum goes via the globus pallidus or substantia nigra, as shown in figure 2(A). The GPi of primates (or the EP in rats), together with the SNr, innervate areas of the thalamus which, in turn, project to the cortex, completing a cortical–basal ganglia–cortical circuit. The GPe is involved in a second re-entrant circuit with the STN, which projects back to both segments of the globus pallidus and the SNr.

The pattern of firing activity in projection neurones changes through successive output stages of the basal ganglia, from the sparsely distributed and infrequent episodes of firing which are typical of the striatal spiny projection neurones, to tonic high frequency firing with brief reductions in firing rate among the pallidal neurones, to phasic increases in activity in subthalamic neurones associated with movements citeref:232. These features suggest that information is encoded in different ways: as a sparsely distributed code involving many neurones in the striatum and as a more compressed temporospatial code involving fewer neurones in the pallidum, as illustrated in figure 2(B).

The most influential anatomical and physiological studies emphasize that several segregated basal ganglia thalamocortical pathways exist [9]. However, it is not clear how much segregation is maintained in circuits which pass through several stages of convergence [6, 181, 204]. In passing through successive stages of the rat basal ganglia the number of neurones in each stage decreases from about 3 000 000 in the striatum, to about 40 000 in the globus pallidus, to about 12 000 in the subthalamic nucleus [173], a ratio of about 250 : 60 : 1 (see figure 1(A)). The preservation of functional specificity indicated by single cell electrophysiological studies is much greater than expected from the reduced numbers of neurones at each stage. Some kind of ‘dynamic focus’ is implied [181, 182, 183]. This may be best understood in terms of the transformation from sparse spatially distributed coding to compressed temporospatial coding in the output stages of the basal ganglia.

The following subsections consider the cellular and synaptic organization of the output stages of the basal ganglia. The globus pallidus neurones and their connections are considered first. Then the subthalamic nucleus is described. Finally, the output via the thalamus to the cerebral cortex will be considered, together with some informal ideas about the possible functional significance of this unusual circuit.

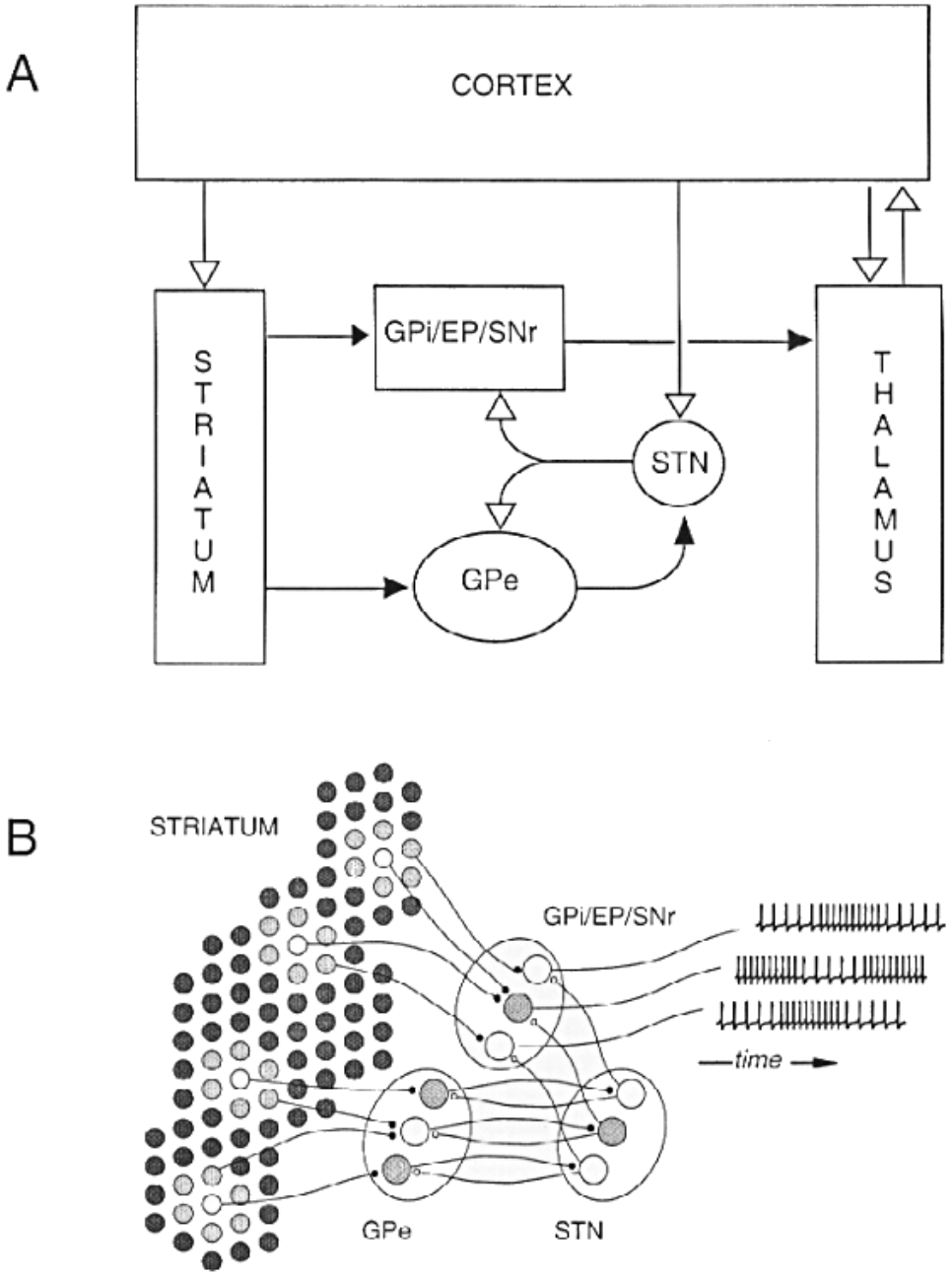

Figure 2. System-level interactions between the cortex, striatum, and pallidal–STN complex. (A) Major interactions indicating the effects of the majority of neurones on target structures. Open arrowheads indicate predominantly excitatory effects. Full arrowheads indicate inhibitory effects. (B) Neural network-level detail of interactions. Large and medium-sized circles indicate pallidal and striatal neurones, respectively. Neurones are depicted as active (open circles); inhibited (grey circles) or quiescent (black circles). Small dots indicate synapses, which may be excitatory (open dots) or inhibitory (black dots). Abbreviations: GPi/EP/SNr, direct pathway nuclei: globus pallidus (internal segment), entopeduncular nucleus, or substantia nigra (pars reticulata); GPe, indirect pathway nucleus, globus pallidus (external segment); STN, subthalamic nucleus.

3.1. The internal organization of the globus pallidus

The output from the striatum forms a prominent axonal tract which terminates in the globus pallidus and substantia nigra [182]. The majority of striopallidal axons use GABA and are inhibitory [65, 169, 177]. The main effect of striatal projection neurones is inhibition of pallidal (and substantia nigra) output neurones [175] resulting in brief interruptions of their tonic firing activity.

The principal neurones of the globus pallidus are large cells with long, thick, generally smooth dendrites that seldom branch [57, 71, 72, 156]. The dendritic tree has a discoid form, with the flat surface oriented orthogonally to the bundles of afferent fibres from the striatum [59, 114, 178]. The pallidal neurones display tonic firing at rates of up to 100 action potentials per second. Their tonic activity is partly due to intrinsic properties of the pallidal neurones [165] and in part to excitatory inputs received from the subthalamic nucleus [75, 116].

Afferent axons from the striatum to the globus pallidus and substantia nigra travel in bundles before giving off collaterals to form fine perpendicular branches [57, 71]. The branches make synapses *en passant* as they run along the dendrites of the pallidal cells [59, 80]. A given striopallidal axon can terminate more than once on a given pallidal cell dendrite. Some axons have short collaterals that run in parallel with the parent axon and seem to contact a single dendrite repetitively [72] though numerous afferent fibres may converge on a given dendrite [66]. This suggests limited divergence, each striatal neurone contacting relatively few pallidal cells, but significant convergence, with many striatal neurones contacting each pallidal cell.

The main targets of the pallidal output neurones are thalamic neurones which project to the cerebral cortex. These are tonically inhibited by the repetitive firing of the pallidal projection neurones. Thus, when the striatal projection neurones fire and inhibit the tonically active pallidal neurones, they release the thalamic neurones from inhibition [56, 140]. There is also an inhibitory projection from the globus pallidus to the subthalamic nucleus [223].

3.2. Subthalamic nucleus

The subthalamic nucleus consists of closely-packed neurones with long, sparsely spiny dendrites radiating from the cell body [45, 110]. Most if not all of the neurones are projection neurones [224]. They receive inhibitory synaptic inputs from the globus pallidus [111, 224] and excitatory inputs from the cerebral cortex [115].

The subthalamic nucleus exerts a powerful excitatory influence on the output structures of the basal ganglia (for example, the substantia nigra and globus pallidus) and has been described as the main driving force of the basal ganglia [110, 112, 116]. Lesions of the subthalamic nucleus produce marked motor abnormalities with conspicuous and disruptive involuntary movements.

About half of the subthalamic neurones have collateral branches which terminate inside the nucleus, presumably making excitatory contacts with other subthalamic projection neurones [110]. Gillies [75] suggested that these collaterals are a key aspect of the functioning of the subthalamic nucleus, and has investigated dynamic aspects by mathematical analysis and computer simulation (see subsection 4.3).

The subthalamic neurones produce irregular, spontaneous firing at 10–20 Hz and occasional spontaneous bursts [74]. They respond to cortical stimulation with an excitation–inhibition–excitation sequence. The inhibitory phase of the sequence appears to be due to their pallidothalamic inputs. In the intact animal they respond with increases in firing to

externally imposed movements. Their firing in relation to self-initiated movements has not been reported, but in tracking tasks they typically fire soon after the onset of a movement, suggesting a role in termination rather than initiation [232].

3.3. Output from the basal ganglia to the cortex

The outflow from the striatum in primates goes in large part via motor areas of the thalamus. The pallidothalamic and nigrothalamic pathways terminate in specific zones in the thalamus [6, 43]. The medial pallidum gives rise to the ansa lenticularis and the lenticular fasciculus which project to the ventral anterior and ventral lateral nuclei of the thalamus [44, 89, 125]. Neurones in these regions of the thalamus project in turn to the supplementary motor cortex [196, 210] premotor cortex [166] and medial prefrontal cortex and anterior cingulate cortex [76, 166]. The nigrothalamic pathway also terminates in the thalamus [90, 187] in areas with more widespread projections to large areas of the frontal association cortex [90, 187]. In subprimates there is a greater degree of overlap in the terminations of the pallidal and nigral pathways in the thalamus [88, 90].

The overall effect of striatal output on thalamic neurones has been studied in several experiments. Individual nigrothalamic cells receive an inhibitory influence from a preferential striatal locus [56]. Stimulation of the striatum produces a focus of inhibition in a restricted number of globus pallidus neurones, with a contrasting surround of excitation at the fringes [222]. Application of glutamate outside the inhibitory striatal area is either ineffective or results in an excitatory effect. From a given striatal area, both excitatory and inhibitory influences can be exerted simultaneously on two distinct nigrothalamic neurones. The activation of a given projection neurone is triggered only by a restricted portion of the striatum [56]. These features suggest that a high degree of functional specificity is preserved throughout the striatal outflow pathways. (See also [81]).

Excitation of the striatum produces a time-locked increase of activity in a large number of thalamic cells projecting to the motor cortex [56]. Two patterns of termination of thalamocortical fibres have been described in the rat cortex [14]: some terminal axons are limited to a small area in motor cortex, with boutons both in deep and surface layers, while others run for several millimetres parallel to the surface and immediately below it. Synapses are made with dendritic spines on the cortical pyramidal neurones. Stimulation of the thalamocortical fibres produces excitatory postsynaptic potentials throughout the depths of the motor cortex [119, 207]. Thus, the net result of striatal output on the cerebral cortex is release of corticothalamic–thalamocortical loops from inhibition: an effect referred to as disinhibition [117]. These processes are illustrated in figure 2(B).

3.4. Circuit properties

The circuits of the output stages of the basal ganglia raise some intriguing questions. How should we interpret the order-of-magnitude differences in the numbers of neurones at successive stages of the basal ganglia [173, 199, 221]? Is there some kind of compression of information into fewer and fewer channels? What should we make of the inhibitory projections between nuclei, with three such connections in apparent series [56, 66]? Are these simply devices to invert the sign of outputs, so that inhibitory interactions can occur among output neurones and then be converted back to effectively excitatory outputs? Or, can we make a more interesting conjecture, say, in terms of pulsed outputs [75]? What is needed are ideas about signal processing that go beyond simple notions of convergence or segregation.

The feedback pathway between the cerebral cortex and basal ganglia suggests a possible role in the regulation of overall levels of activity in the cerebral cortex [33]. The overall positive sign of this circuit suggests that it might contribute to the activation of cortical cell assemblies. It has been suggested that one function of the focussing effects of the basal ganglia may be to deepen the basins of attraction around selected cortical activity states [236]. However, these informal suggestions require rigorous development before they can be called models. Existing models of different components of the basal ganglia are considered in the following section.

4. Computational models of basal ganglia circuits

According to Marr in his work on vision [143] a first step towards understanding how a nervous system works is to characterize the computational problem the system is attempting to solve. It is clear that much less is known about computations in the basal ganglia than about the computational problems of vision. We cannot depend on concepts of basal ganglia function based on clinically observed deficits or loss of function after experimental lesions, because such deficits are not necessarily the inverse of the normal function [228]. Thus, it may be a mistake at this stage to project a computational function on to the basal ganglia.

An important contribution that computational models could make, in principle, would be to formalize the transformation the basal ganglia performs in order to produce outputs from inputs. Ideally, we should have some idea of how to interpret the signals in the afferent and efferent pathways. This is diicult, because the afferents arise from all cortical areas, sensory and motor, and the efferents project to regions of the cortex whose operation is also poorly understood, such as the supplementary motor area. Some understanding may be gained from a bottom up analysis of structure and its implications for transformation of information.

Models of basal ganglia structure and operations are in an embryonic stage. The following review focuses on those models with a direct link to biological data.

4.1. Synaptic and cellular models

The properties of the spiny projection neurone are central to the operations performed by the striatum on its input from the cortex. To a first approximation, the striatum is an array of spiny projection neurones forming a single layer between the cortical inputs and the striatal outputs.

The transformations performed in the dendritic spines, dendrites and cell body of these neurones have been investigated in a detailed model described by Wilson [250, 255]. The properties of dendrites are particularly important in the spiny neurones of the striatum [246]. Corticostriatal synaptic responses are attenuated by the effects of dendritic spines and electrotonically long dendrites [243]. Input resistance varies with membrane potential, largely determined by potassium channels activated by hyperpolarization. Thus, neither the cell membrane resistance nor the charging time are constants: Both vary considerably with membrane potential, giving the cell distinctive nonlinear properties with profound implications of synaptic integration in these neurones [146, 247].

The actions of tonically active dopamine neurones can be incorporated into the properties of spiny neurones by modifying sodium, potassium and calcium channels appropriately. Currently, there is little modelling work published in this area [146, 167, 205, 206] but with advances in the detailed description of channel properties in striatal neurones [211, 212, 213, 214], considerable activity is likely in the near future.

A better understanding of the effects of phasic bursts of activity in dopamine neurones on synaptic levels of dopamine has come from the use of detailed models in the interpretation of measurements of dopamine overflow from the synaptic cleft [96, 100]. Although there are tonic low-level concentrations of dopamine in the extracellular fluid surrounding striatal neurones, high frequency activity in the axons is predicted to induce micromolar concentrations of dopamine in the synaptic cleft, lasting only fractions of a second. These synaptic effects of dopamine are the ones most likely to be relevant to the phasic activation of dopamine neurones by rewarding stimuli.

4.2. Striatal network models

Initial models of the striatal network were based on anatomical and neurochemical characteristics of the spiny projection neurones. Their six primary dendrites radiate from the soma in three dimensions, and divide several times to form a dendritic tree which occupies a spheroidal region with a long axis diameter of approximately 500 μm [26]. The local collaterals of the axons have a similar arrangement and form an extensive plexus mainly restricted to the space of the dendritic field of the neuron [186]. Estimates of the existence and strength of synaptic connections based on the degree of overlap of axonal and dendritic fields of adjacent neurones led to a homogenous network model with symmetric (reciprocal and equal) local inhibitory connections [237].

The idea of local symmetric inhibitory connections among spiny projection neurones was extended by suggesting that the functional unit of striatal function was a domain of mutual inhibition, defined as a subset of striatal neurones with reciprocal inhibitory connections [237]. Figure 3 illustrates the proposed domain of inhibition. The number of neurones in

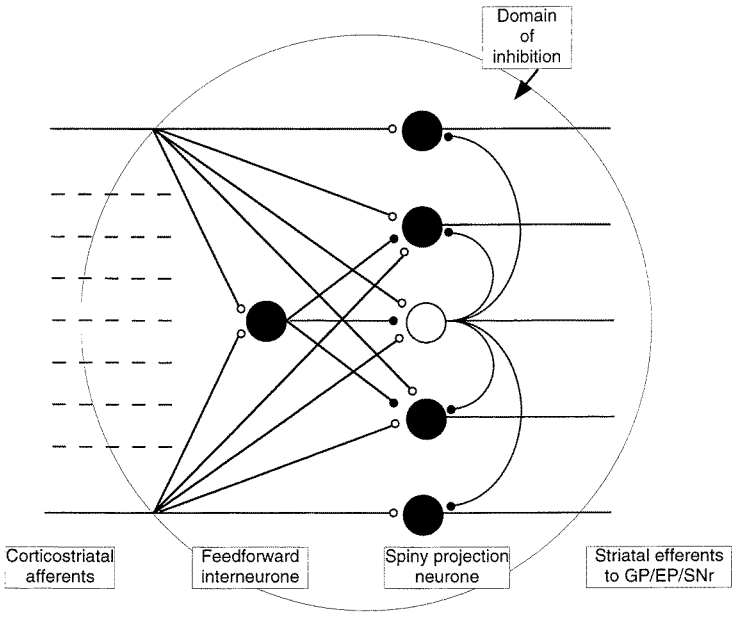

Figure 3. Domain of inhibition. Corticostriatal afferents are shown converging on a GABAergic feedforward interneurone and a set of spiny projection neurones. The active projection neurone is depicted as an open circle, inhibiting neighbouring spiny projection neurones.

a domain was estimated to be around 720, but it was assumed that only a subset of these would actually make connections, and thus there would be several disjoint sets of about 100 neurones in each potential domain [236, 237]. These estimates were based on cell density measurements in human material, and the numbers for the rat striatum are correspondingly smaller [173].

The prevailing dynamic within a single, isolated domain, as determined by numerical simulations and mathematical analysis, is likely to be one of competition, in which the more active neurones suppress activity in their less active neighbouring spiny neurones [10, 237]. Across a network composed of multiple, overlapping domains, the characteristic activity produced by uniform excitatory input is predicted to consist of stable, spatially localized peaks of high activity (produced by a small number of neurones) surrounded by valleys of inactivity (representing a larger number of quiescent neurones). This basic pattern is a robust property of the model, and occurs in networks of different sizes and topologies (for example, analogous activity distributions were present on a 1D and a 2D torus).

The effects of dopamine and acetylcholine inputs were represented in the model by variations in a membrane potassium conductance under dopaminergic–cholinergic control. This conductance could switch the behaviour of the striatal network between two dynamic modes: competition and coactivation [10]. Competition has already been defined. In coactivation, there is a uniform distribution of activity among all the neurones. The mode of competition is assumed to be the normal mode in which the striatum operates during free movements of the limbs, while the mode of coactivation may correspond to the state of muscular rigidity which occurs as a symptom of Parkinson's disease, or perhaps under normal conditions when fixation of a limb is required. The effect of dopamine is to promote a dynamic mode of competition, and when dopamine is deficient the competitive mode breaks down into one of coactivation. In principle, the model provides a link between the effects of dopamine deficiency and the symptom of muscular rigidity brought about by coactivation of mutually antagonistic groups of muscles.

Some experimental evidence for two dynamic modes of striatal function under dopaminergic-cholinergic control exists. Reciprocal zones of excitation and inhibition have been described after the injection of an excitatory amino acid into a small locus of the striatum [188]. This finding is consistent with the idea of competition. Systemic injection of the dopamine antagonist drug haloperidol abolished these reciprocal zones of excitation and inhibition [188]. It has also been reported that stimulation of the striatum produces a focus of inhibition in a restricted area of the globus pallidus, with a contrasting surround of excitation at the fringes [222]. When dopaminergic activity is reduced by making chemical lesions of the dopaminergic neurones there is a loss of focus of the inhibition produced in the pallidum by striatal stimulation [68]. Thus, there is some evidence suggesting that a competitive dynamic occurs in the normal striatum and that it can be switched to coactivation by dopamine antagonists.

The relation between coactivation of striatal output neurones and rigidity is somewhat speculative. Electrophysiological studies have shown that striatal neurones with movement-related activity related to movements often occur in clusters related to movements about a single joint. These clusters are physically of similar size to the proposed domains. Activating the output neurones within these zones, using stimulation currents in the microampere range, produces discrete movements of individual body parts, usually restricted to a single joint [7, 8]. Coactivation of many or all the neurones within a zone may produce cocontraction of antagonistic groups of muscles around a joint, which might thus cause muscular rigidity.

One of the critical assumptions of the model just described is the existence and symmetry of inhibitory connections among spiny neurones. This assumption was based on the

argument that the strength of connections between neurones is related to the degree of overlap of their axonal and dendrite fields. Thus, the degree of symmetry of connections depends on the extent to which axonal and dendritic arbors have a radially symmetric and concentric arrangement about the soma. Although most evidence from histological investigations is consistent with the assumed symmetric and homogeneous connectivity among striatal output neurones, there is known to be variation in the shape of the dendritic tree of the medium spiny neurones [102]. For example, some neurones in the normal striatum have flattened dendritic trees [180, 226]. Also, in a number of diseases the dendritic architecture of the spiny projection neurones can become distorted. The connectivity in such cases may not be symmetrical.

Marked variations in the shape of the dendritic tree of the medium spiny neurones occur in the early-stages of Huntington's disease [67, 77]. Instead of coursing radially outward as in the normal striatum, the dendrites are often bent back towards the cell body, or distorted in other ways by abnormal growth and degeneration. Therefore, in Huntington's disease the connectivity is almost certainly asymmetric in many of the surviving neurones.

Computer simulations of the striatal network using asymmetric connectivity show how abnormal bursts of neural activity could be caused by a change in the shape of the dendritic trees [241]. Three different network topologies were studied, each based on different assumptions about the synaptic connectivity among spiny neurones. In all networks neurones were interconnected by inhibitory synapses. The connectivity was either symmetric, in which case all connections between cells were reciprocal and equal in strength, or asymmetric. Simulations showed that networks with symmetric connectivity receiving randomly distributed afferent excitation produced stationary spatial activity patterns. In contrast, asymmetric connectivity in homogeneous networks produced slow travelling-wave activity across the network. These results suggested changes in the shape of spiny neurones caused by Huntington's disease would result in slow travelling-wave activity.

It is difficult to predict the movements that would result from slow travelling wave activity in the striatum. Such activity might produce strong output activity from the basal ganglia. This together with a patchy, somatotopic representation of bodily movements in the striatum could produce involuntary movements like that seen in Huntington's disease. When the connectivity is inhomogeneous as well as asymmetric, the activity becomes irregular, with bursts of activity of variable duration occurring in apparently random order.

The results of the computer simulation are compatible with several pieces of evidence which suggest that abnormal firing of the surviving neurones in Huntington's disease may underlie the symptom of chorea. Firstly, some Huntington's disease patients suffer from chorea before any loss of neurones from the striatum can be detected [164]. Secondly, although an excitotoxic lesion of the striatum can reproduce the neuropathology of Huntington's disease very well, loss of neurones is not sufficient to produce the symptom of chorea [51, 98]. Thirdly, the bursts of activity produced in the model resemble those seen in animal models of Huntington's disease in which excitotoxic lesions combined with dopaminergic drug administration produce abnormal bursts of activity in the surviving neurones that are associated with choreiform movements [97, 98].

A completely different computer simulation model has been proposed by Connolly and Burns [46, 47, 48], based on electrotonic coupling between striatal neurones. In their model each neurone in the striatum represents a point in a particular state space. For example, such a point might represent a joint angle or hand position. They propose that the electrotonic coupling between striatal neurones ensures smooth transitions between state spaces which could be used to control movement [46]. Their model also proposes that the loss of medium spiny neurones in the striatum in Huntington's disease can contribute to the symptoms. The

missing neurones make the network coarser and cause jerkier movements because of the holes in the state space representation.

4.3. Pallidal–subthalamic system

Gillies [75] described a model of the subthalamic nucleus. Based on detailed estimates of local interconnections among subthalamic output neurones, the model represents the nucleus as densely interconnected network of excitatory neurones. Analysis of a simplified version of the model shows that it is likely to exhibit two-state behaviour in a physiological range of parameter values. In response to excitation from the cerebral cortex, localized regions of the nucleus are likely to respond with a phasic burst of firing activity, that is sustained until terminated by some other mechanism. One mechanism for termination of the activity involved transient calcium channels, considered in more detail in a single cell model and a computer simulation [75]. Another suggested mechanism was inhibition from the globus pallidus inputs.

The overall picture of the operation of the subthalamic nucleus suggested by Gillies [75] is that the response of large regions of the nucleus should take the form of a pulse of activity with a sharp rise and fall. This leads to the idea that the subthalamic nucleus acts as a braking mechanism inducing a wide-spread pulse of inhibition in a two-pulse sequence, producing a window of disinhibition with width under striatal control. It is conceivable that such a mechanism may be involved in such motor functions as scaling of the initial agonist burst in a ballistic movement.

4.4. Cortical–basal ganglia circuits

A number of models have been proposed for the basal ganglia which are based on a network model proposed by Jordan [95]. His model is basically a three-layer feedforward network, with a feedback connection from the output units to a subset of the input units. The feedback connections make it possible to generate sequences. It can be taught particular sequences by a back-propagation learning algorithm [193]. Several authors have proposed models based on such networks [31, 34, 61, 162].

Projecting parallel distributed processing models of psychological processes directly onto the basal ganglia is fraught with possible difficulties. The anatomy does not always match, and some interesting features may be lost from the analysis. Such features include: inhibitory pathways connected in series, recurrent interactions within particular nuclei, distinctive nonlinear properties of neurones, and the ratios of neurones in different nuclei. The use of back-propagation algorithms to adjust connectivity is also problematic. For example, back-propagation learning rules require synapses which may be modified according to the partial derivative of the error in an output signal (with respect to the synaptic weight). It is not known what the output signal should be in terms of neural outputs from the basal ganglia, so it is difficult to calculate the error signal. Furthermore, a literal interpretation of the models requires specific connections between the mechanism which detects an error, and each individual synapse. There is no evidence that such connections exist in the basal ganglia. As noted by Donohoe and Palmer [62] ‘On the contrary, the neural systems mediating selection by reinforcement appear to be non-specific systems that project diffusely within the brain areas they serve’.

There seems to be a gap in the literature and a need for large-scale models of the basal ganglia that are based on the actual anatomy and physiology of the component neurones. Such models would be a major long-term undertaking. Preliminary work in this area has

appeared [30, 185], but further work is needed if the computations performed in these circuits are ever to be elucidated.

5. Conclusions

Previous models have contributed to a better understanding of the computations performed by the basal ganglia. This is especially true where they have been tested experimentally and refuted [92], disputed [15, 179, 239] or corrected [173]. Models based on the actual anatomy and physiology are likely to be appreciated by the basal ganglia community, who increasingly recognize the contribution such models can make [78].

Some links between the symptoms of basal ganglia disorders such as Parkinson's disease and Huntington's disease, and the underlying mechanisms have been suggested. However, less progress has been made towards modelling the normal functions of the basal ganglia. This is made difficult by the lack of a simple description of the operations performed by the striatal circuits. It may be the case that such a description can only be reached by an iterative process combining bottom-up descriptions of circuit properties and top-down

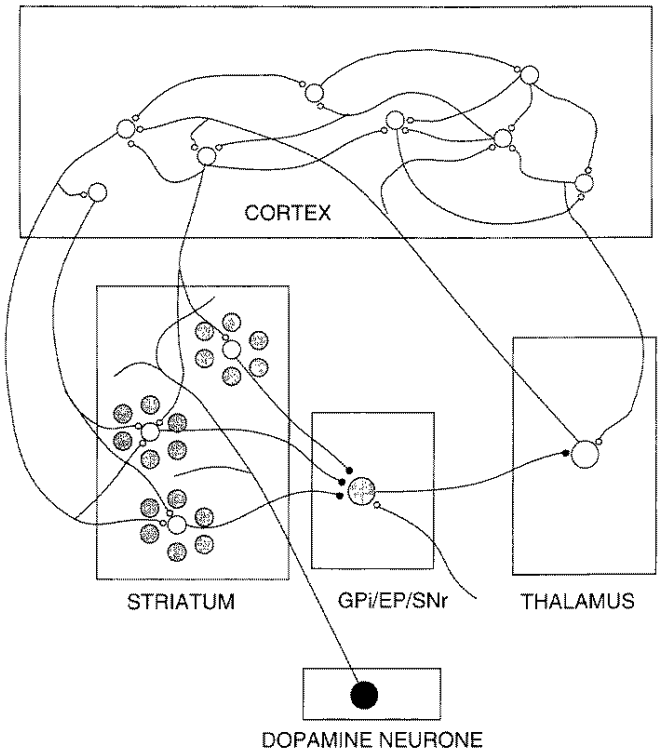

Figure 4. Corticostriatal interactions. A cortical assembly excites a subset of striatal neurones which converge on a particular pallidal cell. The disinhibitory effect of the striatal neurones on the thalamus results in selective amplification of the activity of the active assembly. Dopaminergic input, produced in response to a favourable outcome of the cortical assembly activity, can strengthen the active corticostriatal connections. The overall effect is to make the cell-assembly more likely to ignite in a similar situation in the future. Modified from Miller and Wickens [154].

hypotheses based on the effects of selective lesions on behaviour and descriptions of neural activity in awake animals.

The evidence reviewed suggests that the basal ganglia play a role in learning on the basis of reinforcement. A possible mechanism for this is a three-factor rule for synaptic modification of the cortical inputs to the striatum. The operation of this mechanism would increase the activity of striatal neurones receiving inputs from cortical neurones, in particular those corticostriatal neurones responding to the previous antecedent of reward.

In going from a cellular model of reinforcement to a theory which explains how these mechanisms bring about adaptive changes in behaviour, it is necessary to consider a larger scale picture in which the basal ganglia and cortex interact (see figure 4). Intrastriatal mechanisms ensure that few striatal neurones become active at any one time, these being a subset that are excited by cortical activity patterns that have been repeatedly associated with reward in the past. The spatially distributed firing patterns of these neurones are transformed by pallidal and nigral mechanisms, into a temporally coded output to the thalamus. The release of thalamocortical neurones from tonic pallidal and nigral inhibition results in increased activity of cortical neurones, which may either intensify the existing pattern of cortical activity or switch it to a new pattern by activating an alternative. Repeated iterations of this process may converge on the activation of a cortical assembly representing the action that on the basis of the accumulated effects of synaptic modification in the corticostriatal pathway is predicted to be most likely to produce a favourable outcome for the animal. The contribution of the basal ganglia thus appears to be to select and activate cortical activity patterns that have been associated with reinforcing outcomes in similar situations in the past.

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