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Basal Ganglia

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Introduction

Lying either side of the forebrain/midbrain boundary, at the hub of the mammalian brain, the basal ganglia are a group of highly interconnected brain structures with a critical influence over movement and cognition. The importance of these nuclei for a cluster of human brain disorders including Parkinson's disease, Huntington's disease, and schizophrenia, has produced a century or more of strong clinical interest, and a prodigious volume of neurobiological research. Given the wealth of relevant data, and a pressing need for a better functional understanding of these structures, the basal ganglia provide one of the most exciting prospects for computational modelling of brain function.

This article will begin by summarising aspects of the functional architecture of the mammalian basal ganglia and then describe the computational approaches that have been developed over the course of the past decade (see also Houk, Davis, and Beiser, 1995; Wickens, 1997; Gillies and Arbuthnott, 2000). An important task for an appraisal of computational models is to provide a framework for comparing pieces of work that can differ radically in their breadth of focus, level of analysis, computational premises, and methodology, and whose relative merits can consequently be difficult to ascertain (see LEVELS OF ANALYSIS). Here, we first distinguish between models that attempt to incorporate appropriate biological data (anatomical and/or physiological) and those that attempt an explanation of function using generic neural network architectures. In this review we limit ourselves to just those models that incorporate known neurobiological constraints and consider some of the implications for these models of recent biological data. Second, we divide models into two main levels of analysis: (i) those that work at a comparatively low level of detail (membrane properties of individual neurons and micro-anatomical features) and which restrict themselves to a single component of the basal ganglia nucleus; and (ii) those that deal at the 'system-level' with the basal ganglia as a whole and/or with their interactions with related structures (e.g. thalamus and cortex). Third, we seek to classify system-level models in terms of the primary computational role that they suppose is being addressed by the neural substrate.

The neuromodulator dopamine is known to play a vital role in regulating basal ganglia processing and also in mediating learning within the basal ganglia. Whilst some of the likely regulatory functions of dopamine will be considered below, a fuller discussion of this topic, including hypotheses and models concerned with the role of dopamine in learning from reinforcement, are the subject of a separate article (THE ROLES OF DOPAMINE).

Key architectural features

There have been many excellent summaries of the functional anatomy of the basal ganglia (e.g. Mink, 1996; Smith, Bevan, et al., 1998), the following therefore focuses on those aspects most relevant to understanding the models discussed below.

The principle structures of the rodent basal ganglia (Figure 1) are the striatum (consisting of the caudate, the putamen, and the ventral striatum), the subthalamic nucleus (STN), the globus pallidus (GP), the substantia nigra (SN), and the entopeduncular nucleus (EP) (homologous to the globus pallidus internal segment in primates). These structures are massively interconnected and form a functional sub-system within the wider brain architecture. There is a growing consensus that the basal ganglia nuclei can be regionally subdivided on the basis of their topographically-organised connectivity with each other and with cortical and thalamic regions. Current views of information processing within the basal ganglia are heavily influenced by this suggestion of multiple parallel loops or channels.

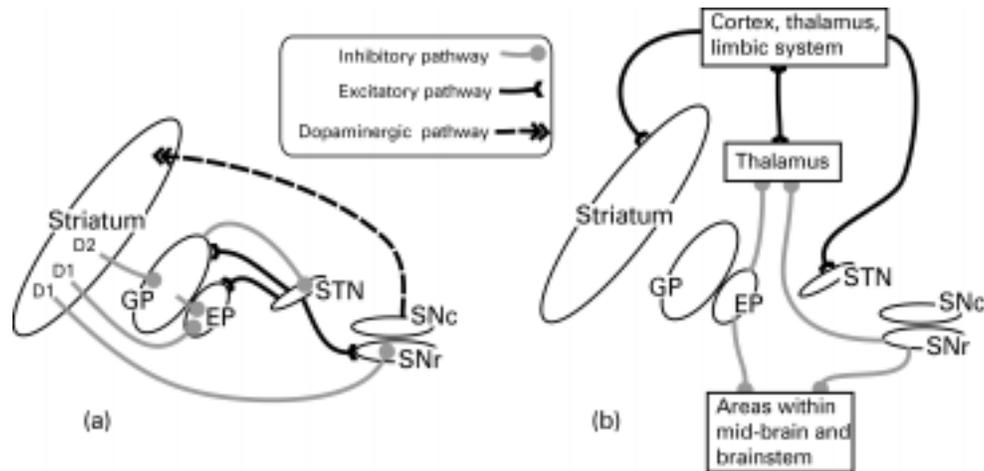


Figure 1. Basal ganglia anatomy of the rat: (a) internal pathways, (b) external pathways. Excitatory and inhibitory pathways are denoted by solid and grey lines respectively; not all connections are shown. See text for key to abbreviations.

The principle input components of the basal ganglia are the striatum and the STN. Afferent connections to both of these structures originate from virtually the entire brain including, cerebral cortex, many parts of the brainstem (via the thalamus), and the limbic system. Input connections provide phasic (intermittent) excitatory input.

The main output nuclei of the basal ganglia are the substantia nigra pars reticulata (SNr), and the entopeduncular nucleus (EP). Output structures provide extensively branched efferents to the thalamus (which project back to the cerebral cortex), and to pre-motor areas of the midbrain and brainstem. Most output projections are normally (tonically) active and inhibitory.

To make sense of the intrinsic connectivity of the basal ganglia it is important to recognise that the main projection neurons from the striatum (medium spiny cells) form two widely distributed populations differentiated by their efferent connectivity and neurochemistry.

One population comprises neurons with mainly D1-type dopamine receptors and projects to the output nuclei (SNr and EP). In the prevailing informal model of the basal ganglia (Albin, Young, and Penney, 1989) this projection constitutes the so-called *direct pathway* to the output nuclei (see figure 2a). Efferent activity from these neurons suppresses the tonic inhibitory firing in the output structures which in turn *disinhibits* targets in the thalamus and brainstem.

A second population of striatal output neurons has predominantly D2-type dopamine receptors. This group projects primarily to the globus pallidus (GP) whose tonic inhibitory outputs are directed both to the output nuclei (SNr and EP) and to the STN. The inhibitory projection from D2 striatal neurons constitutes the first leg of an *indirect pathway* to the output nuclei. Since this pathway has two inhibitory links (Striatum–GP, GP–STN), followed by an excitatory one (STN–EP/SNr), the net effect of striatal activity is to activate output nuclei which increases inhibitory control of the thalamus and brainstem.

The main source of dopamine innervation to the striatum is the Substantia Nigra pars compacta (SNc). Interestingly, the D1 and D2 striatal populations respond differently to dopaminergic transmission, activation of D1 receptors having a predominantly excitatory effect while D2 receptor activation appears to be mainly inhibitory. This arrangement seems to provide dopaminergic control of a 'push/pull' mechanism subserved by the direct (inhibitory) and indirect (net excitatory) basal ganglia pathways. Importantly, a key input to the SNc is from striatal areas known as striosomes (areas that project to EP/SNr are known as matrisomes), thus the striatum is a major player in modulating its own dopaminergic input.

Whilst the above description focuses on pathways originating from the striatum, the STN, though much smaller in size, is increasingly recognised as a second important input structure within the basal ganglia

functional architecture (see Mink, 1996). STN's excitatory outputs project to both the output nuclei (SNr and EP) and to the intermediary structure GP.

Recent anatomical data by Wu et al. (2000) has suggested that the 'direct pathway' is actually branched with a significant output going to GP. Other new data shows the existence of additional inhibitory projections from GP to EP/SNr implying a multiplicity of indirect pathways (Smith, Bevan, et al., 1998). The proliferation of intrinsic basal ganglia circuitry in recent literature has highlighted the need for: (i) a radical reinterpretation of basal ganglia functional anatomy; and (ii) an increasingly important role for computational modelling in interpreting the functional properties of the multiple interconnections and loops within the basal ganglia.

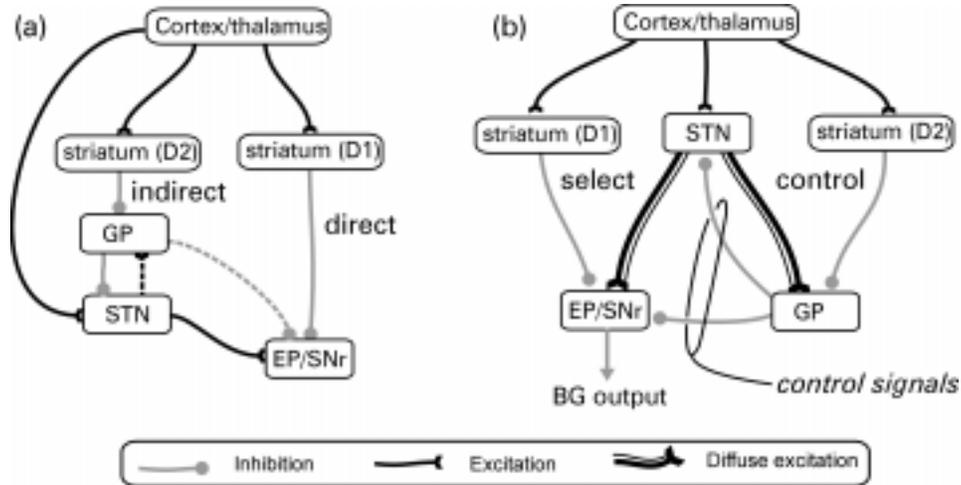


Figure 2. Functional interpretations of the basal ganglia: (a) *informal* models stress the 'direct' and 'indirect' pathways and leave the functional consequences of their interactions ill-defined, other pathways (indicated by dotted lines) have until recently received less emphasis; (b) an alternative interpretation arising from *computational* modelling by Gurney et al. (2001) specifies specific functional roles for the various intrinsic basal ganglia connections summarised by the concept of 'selection' and 'control' pathways. See text for further explanation.

Low level models of individual basal ganglia nuclei

In contrast to the diverse nature of the brain regions projecting to the mammalian striatum, its internal organisation appears surprisingly homogeneous. This finding offers hope that an understanding of striatal functioning in one local area could generalise across much of the entire structure. At any given moment the majority of striatal cells are in an inactive 'down-state', and can only be triggered into an active 'up-state' (where they can fire action potentials) by a significant amount of coincident input. Since each neuron has a wide dendritic fan-in (with up to 30,000 synapses), but only a few synapses with any single source neuron, it must receive coincident signals from a large population of inputs to become active (see Wilson in Houk et al., 1995). This organisation suggests that striatal spiny neurons may act as 'context-specific filters', each one configured to match a specific pattern of activity distributed across multiple loci in one or more brain areas (Mink, 1996).

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 (see Oorschot et al. in Nicholson and Faull, 2002). Wickens and colleagues (see Wickens, 1997) have investigated the dynamics of such local neighbourhoods of striatal neurons using network models. Under varying assumptions of topology and size, they concluded 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 neighbours. This research also examined the effects of simulated dopamine inputs, showing that under circumstances of low dopamine, the dynamic of the network changes from competition to coactivation (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. Using another variant of this model, Wickens explored the implications of dendritic asymmetries based on those observed in the early stages of Huntington's disease. Simulation of asymmetric interconnectivity generated slow travelling waves of activity (where normal symmetric configurations produce stationary activity patterns), suggesting that a similar abnormal network dynamic may underlie the sudden involuntary movements seen in Huntington's patients.

Apart from the striatum, relatively little attention has been given to modeling intrinsic processing within basal ganglia nuclei. One interesting exception is the work by Gillies and Willshaw (see Gillies and Arburthnott, 2000) on a model of the STN. Having incorporated key physiological and anatomical properties, they showed that the widespread excitatory interconnectivity between STN neurons allows focused input to produce a widely distributed pulse of excitation to SNR and EP. Given that the output of the basal ganglia is largely inhibitory, phasic STN activity could serve to break established patterns of activity in basal ganglia targets thereby acting as a form of interrupt or 'reset' mechanism.

The above models have as their starting point a wealth of low-level biological constraints with the rationale that the resulting model behaviour must approximate observed biological data. Nevertheless, since the phenomena discussed are related to the ability to resolve localised competitions (in striatum) and to interrupt ongoing behaviours (STN), we would argue that these models may be thought of as addressing components of the overall computational problem of action selection (see further discussion below).

System level models of basal ganglia circuits and external functional loops

Most of the effort so far directed at basal ganglia modeling has been concerned with simulating interactions between the various basal ganglia structures, and between the basal ganglia and other key brain regions such as cortex, thalamus, and brainstem. A comparatively high level of abstraction is usually adopted in this work, in which components of the basal ganglia are decomposed into functional units (e.g. multiple parallel channels). Most work to date has focused on a number of related computational hypotheses—that the basal ganglia function to (i) regulate the degree of action gating, (ii) select between competing actions, (iii) sustain working memory representations, and (iv) store and enact sequences of behaviour. These ideas will be the main focus of the remaining discussion.

Action gating

A key function of the striatum is to provide intermittent, focused inhibition (via the 'direct pathway') within output structures which otherwise maintain inhibitory control over motor/cognitive systems throughout the brain. This architecture strongly suggests that a core function of the basal ganglia is to gate the activity of these target systems via the mechanism of disinhibition. Many basal ganglia models employ selective gating, however, that of Contreras-Vidal and Stelmach (1995) is particularly interesting as it explores gating operations in both normal and dysfunctional model variants. These authors coupled a simulation of basal ganglia intrinsic circuitry to a neural network that computed arm movements. Excitatory striatal input resulted in a smoothly varying signal to thalamic targets that provided the "GO" signal for the motor command, and also set its overall velocity. The time taken to execute movements decreased with increasing basal ganglia input thereby matching the results of striatal microstimulation studies. A 'dopamine depleted' version of the model exhibited akinesia and bradykinesia similar to that observed in Parkinson's disease.

Selecting between competing actions

The proposal that the basal ganglia act to resolve action selection competitions 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, 1999). Multiple selection mechanisms embedded in the basal ganglia could resolve conflict between competitors and provide clean and rapid switching between winners. First, the up/down states of the striatal neurones 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 focussed inhibition from striatum with diffuse (divergent) excitation from STN

could operate as a feed-forward, off-centre/on-surround network across the basal ganglia 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 organising principle, Gurney et al. (2001) have proposed a reinterpretation of basal ganglia functional anatomy in which the direct/indirect classification is replaced by a new functional grouping based on *selection* and *control* circuits (see Figure 2b). Specifically, the focused D1 inhibitory pathway from striatum to EP/SNr (originally the ‘direct pathway’), together with a *diffuse* excitatory pathway from STN to EP/SNr, form a primary feed-forward *selection* circuit. A second group of intrinsic connections centred on the GP acts as a *control* circuit to regulate the performance of the main selection mechanism. Analytical and simulation studies of this model suggest two likely functional roles for this control circuit. First, the inhibition of STN by GP constitutes a negative feedback path that automatically scales the excitatory output of the STN with the number of channels. Second, GP inhibition of EP/SNr forms part of a mechanism that supports dopaminergic regulation of selection. Specifically, increased dopamine in these circuits promotes ‘promiscuous’ selection in which channels are more easily disinhibited, whilst reduced dopamine results in a ‘stiffer’ competition in which there are fewer winners and higher levels of general target inhibition. The adequacy 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 behaviours (see Prescott, Gurney et al. in Nicholson and Faull, 2002). This work confirmed that the simulated basal ganglia can provide effective action selection in a real-world context requiring appropriate and timely behavioural switching. The robot model also provided an insight into the emergent consequences of abnormal dopamine modulation of action selection. For instance, and reminiscent of some motor symptoms of Parkinson’s disease, reduced dopamine was found to cause failures to select appropriate behaviour or to complete behaviours once selected.

An earlier model of the basal ganglia proposed by Berns and Sejnowski (1995) shared the ‘action selection’ premise of Gurney et al., but emphasised possible timing differences between the direct and indirect pathways in a model that included just the feed-forward intrinsic basal ganglia connections. An interesting feature of this model is that it incorporated a version of the dopamine hypothesis for reinforcement learning (see ROLES OF DOPAMINE) as a means for adaptively tuning the selection mechanism.

Sustaining working memory representations

The relationship between basal ganglia and cortex is characterised by relatively segregated parallel loops, in which cortical projections to the striatum are channelled through basal ganglia outputs to the thalamus and then back to their cortical areas of origin. The thalamic nuclei in this circuit also have reciprocal, net-excitatory, connections to their cortical targets. This architecture suggests a pattern of cortical–thalamic activity which, once initiated by disinhibitory signals from the basal ganglia, could be sustained indefinitely. Several authors have proposed that this circuit could act as a working memory store (see Houk et al., 1995). An example of this is provided by Arbib and Dominey’s model of basal ganglia control of the primate saccadic eye movement system (see article in Houk et al., 1995). These authors modeled an experimental task in which a monkey is required to make a saccade to a remembered target location. They simulated circuits in which cortical cells in the frontal eye fields were activated by the target, which, in turn, excited a population of striatal neurons specialised for delayed saccades. The basal ganglia loops involving these cells disinhibited their thalamic targets so that the target location was maintained in the cortico-thalamic circuits until the saccade was made.

In our view, the selection and maintenance of specific working memory items can be viewed as an extension of action selection by the basal ganglia to the domain of cognition (selecting from a range of potential cognitive representations those which are to be sustained as working memory). It is interesting to speculate that deficits in this system may underlie the disorders of thought associated with schizophrenia, attention-deficit disorder, and obsessive compulsive disorder.

Sequence processing

A plausible use for the working memory mechanism outlined above would be to link successful selections during the development of behavioural/cognitive sequences. This idea has therefore become a central theme in a number of basal ganglia models. According to Beiser and Houk (1998), sequence encoding can be viewed

as the task of translating a temporal ordering into a spatial pattern of neural activity. They propose that the initial item in a sequence selects the basal ganglia loop whose striatal neurons are most attuned to that context. When this channel is disinhibited the item then becomes encoded as a self-sustaining pattern of cortico-thalamic activity. Later sequence elements are recorded in an identical way, except that, as each new item is added, the cortical activity triggered by its predecessors becomes part of its context (thereby implicitly encoding its position in the temporal order). Rather than recording sequences as spatially distributed patterns, Fukai (1999) has suggested a form of cortical short-term memory for sequences that uses patterns of fast (gamma) and slow (theta) oscillatory activity. Reciprocal inhibition between striatal neurons would allow the basal ganglia to select the first item in such a sequence, whilst other striatal neurons (and their corresponding basal ganglia outputs) would be recruited to maintain the selection of that item for as long as required. Finally, an excitatory burst from STN terminates the movement and signals the transition to the next item in the sequence. Whilst differing considerably in detail, these two models share the premise that the basal ganglia is specialised to 'unpack' a cortical representation of sequential behaviour by selectively gating each of the component movements. Sequence learning is another important theme in basal ganglia modeling. For instance, Dominey, Arbib, and Joseph (1995) have extended their model of delayed saccade control (described above) to include a mechanism for associative and sequence learning (see SEQUENCE LEARNING) based, again, on the hypothesis that dopamine provides a reinforcement learning signal.

Discussion

The above summary demonstrates that basal ganglia modeling is still at the stage of exploring the space of alternative hypotheses, seeking to operationalize theoretical proposals whilst trying to match known neurobiological constraints. As a result, there is now a candidate set of 'global' basal ganglia functions whose computational requirements we are beginning to understand. It remains to be seen to what extent proposed functions are mutually exclusive and to what extent one may be subsumed within another (for instance, action gating can be viewed as an essential component of action selection). Similar considerations apply when appraising models directed at different levels of basal ganglia function. For example, lower-level models of the striatum or STN may, in the future, be imported as fully functional components into higher-level models. However, some system level models are clearly in direct competition with each other as they ascribe different functional roles to local pathways and nuclei. We anticipate that models based on correct computational assumptions will find it comparatively easy to incorporate new biological constraints, which in most cases will improve their accuracy. In contrast, models making mistaken functional assignments will find it increasingly difficult to incorporate additional biological data whilst maintaining their functionality. Future work will therefore require ever closer links between neurobiologists and modelers to refine the models, to formulate questions based on function, and to test the interesting and unforeseen predictions that can emerge from modeling studies.

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