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The basal ganglia: learning new tricks and loving it

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The field of basal ganglia research is exploding on every level — from discoveries at the molecular level to those based on human brain imaging. A remarkable series of new findings support the view that the basal ganglia are essential for some forms of learning-related plasticity. Other new findings are challenging some of the basic tenets of the field as it now stands. Combined with the new evidence on learning-related functions of the basal ganglia, these studies suggest that the basal ganglia are parts of a brain-wide set of adaptive neural systems promoting optimal motor and cognitive control.

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Current Opinion in Neurobiology 2005, **15**:638–644

This review comes from a themed issue on
Motor systems
Edited by Giacomo Rizzolatti and Daniel M Wolpert

Available online 3rd November 2005

0959-4388/$ – see front matter
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DOI 10.1016/j.conb.2005.10.006

Introduction

There is convincing evidence that learning-related functions are central to the role of the basal ganglia in selecting which actions to perform based on updated representations of current context. Increasingly, studies are focusing on how these learning functions are implemented within the framework of circuits internal to the basal ganglia. These circuits are modulated by monoaminergic inputs from the midbrain and by cortico–basal ganglia pathways, and lead into pathways toward the brainstem or recurrently toward the neocortex. Here, we highlight new work on basal ganglia-based learning and the new challenges to current concepts of basal ganglia circuit function. We propose that one over-arching function of the basal ganglia is to promote optimal control of action.

Basal ganglia-based learning

A key idea emerging in the field of basal ganglia research is that cortico–basal ganglia circuits promote learning of action sequences through trial-and-error learning. Three new papers provide convincing evidence for such a concept of basal ganglia function in songbirds [1••,2••] and mammals [3••]. During such trial-and-error learning, the animal (more generally, the agent) first explores the environment: behavior is variable, and reinforcers shape the behavior until it converges on an optimum for that context. Then, exploitation, with repetition of the successful behavior, replaces exploration [4,5]. These new papers support the view [6] that the basal ganglia, guided by the reward-sensitive mechanism of the dopamine-containing neurons of the substantia nigra, could learn and instantiate the behavioral policy, with feedback then leading to on-line adjustment of the behavior by means of a similar mechanism.

In song birds, the anterior forebrain pathway (AFP), akin to a cortico–basal ganglia circuit, is necessary for song learning in young birds, who copy a template of a tutor song during a critical period. The song of the young bird is highly variable, but with practice and feedback, the song becomes stereotyped, as all of us who enjoy bird songs know. In an ingenious set of experiments, Kao *et al.* [2••] demonstrate that the variability that remains in song performance of adult zebra finches requires the AFP, and show that variability in the neural activity in the AFP is tightly correlated with variability in song output. Their key concept is that the AFP can adjust ongoing activity in effector motor pathways by promoting variability in motor output and by providing a bias signal to the motor system.

Olveczky *et al.* [1••] convincingly demonstrate that the AFP controls variability in the song of the young zebra finch. They transiently inactivated the presumed homolog of cortex that receives basal ganglia outflow (LMAN; lateral magnocellular nucleus of the nidopallium). They found that this inactivation drastically reduces the variability typical of the juvenile bird's song. Stereotyped singing also emerges after pharmacologic blockade of LMAN inputs to the motor cortex-like region called RA (robust nucleus of the arcopallium). Together, these papers strongly support the proposal of Doya and Sejnowski [6] that the variability in behavior necessary for reinforcement-based trial-and-error learning is driven by the basal ganglia.

A direct demonstration of learning-related changes in the variability of neuronal firing in the mammalian basal ganglia has now been presented by Barnes *et al.* [3••]. They monitored the activity of ensembles of projection neurons in the sensorimotor striatum as rats learned a conditional T-maze task by trial and error. Their key finding is that during initial learning, task-related spike firing is at first highly variable across the time-scale of the

entire procedure to be learned (the maze run), but then, with further training and over-training, the firing settles into a stereotyped, less variable pattern that emphasizes the beginning and end of the runs. By changing the learning context through extinction and reacquisition training, they demonstrated that this reduction in variability can be successively reversed and reacquired. They propose that the variable striatal firing during learning represents 'neural exploration', followed by 'neural exploitation' after learning has advanced.

Cortico–basal ganglia loop function and learning

It is reasonable, given the reward-related signaling of midbrain dopaminergic neurons, that this dopaminergic input system could 'teach' the striatum (and, hence, the basal ganglia). Several groups [7–10] have further suggested that the basal ganglia could 'teach' the cortex in cognate cortico–basal ganglia loops via striato–pallido–thalamocortical pathways. To test these ideas, it is necessary to record simultaneously, or in close temporal contiguity, from striatal and cortical neurons during behavioral learning. Such studies are at last beginning to appear [11•,12•,13,14•,15], including three on primates.

Brasted and Wise [14•] tracked alternate-day unit activity in the PMd (dorsal premotor cortex) and putamen as highly trained monkeys learned different cue–movement pairs presented in a conditional visuomotor conditioning paradigm. Learning-related changes occurred in the cortical and striatal neurons at roughly the same rates, and these rates of neural change matched the behavioral learning rates of the monkeys. As the authors point out, such concurrent activity would be predicted by models of cortico–basal ganglia loops as having a recurrent, closed loop architecture.

By contrast, Pasupathy and Miller [11•] found that learning-related changes occurred significantly earlier in the striatum (caudate nucleus) than in the cortex (dorsolateral prefrontal cortex) when the cue associations were reversed in a conditional association task performed by over-trained monkeys. Striatal units changed their activity abruptly after the reversals, and fired earlier and earlier during the delay period between cue and response, whereas simultaneously recorded prefrontal neurons changed more slowly and did not have the long lead times. These findings support the proposal that the basal ganglia instruct the cortex [7–10]. The early firing of striatal neurons could reflect the reversal conditions of the experiment [16].

A third study focused on activity in the prefrontal cortex and striatum during performance of a well learned sequential saccade task in which the monkeys made saccades to targets that appeared successively [12•]. On the basis of simultaneous multi-electrode recordings, these authors found the temporal relationship of the activity in functionally related prefrontal and striatal zones to be highly dynamic. The activity of the striatum could either lead or lag that of the cortex, or the two could have nearly simultaneous activation, depending on what part of the task the monkeys were performing, what the cognitive and motor demands of the task were and what cortical area was monitored. These authors suggest that there is not a fixed timing relationship between the neural activities in the neocortex and those in the striatum in neural activities between cortex and striatum.

These findings accord well with models depicting cortico–basal ganglia circuits as working on-line simultaneously in multiple contexts and time-scales. This view is consistent with the production of the circuit variability needed for on-line corrections of already learned behaviors [1••–3••], and is supported by human imaging studies on the development of routine behaviors [17,18].

Reinforcement signals in the basal ganglia

The spike firing of dopamine-containing neurons of the midbrain, now famously appreciated as carrying signals related to reward, has proved to fit remarkably closely the constraints of reinforcement learning theory, including temporal difference (TD) models, even in the complex context of reward delivery. The dopamine-containing neurons code a reward-prediction error in their phasic firing and appear also to code the uncertainty of the prediction in their maintained firing levels [19] (but see Niv *et al.* [20]). Their phasic firing matches, quantitatively, a positive (but not negative) reward-prediction error [21,22], and reflects both the reward magnitude and the probability of that reward (thus coding expected reward value) in addition to motivational state [23]. This enables the dopamine-containing neurons to tune their range of sensitivity [24] and to exhibit context-dependence [25•]. Aversive stimuli do not appear to activate dopamine-containing neurons (in the rat ventral tegmental area) [26]; and in Parkinson's disease patients, dopamine agonist treatment improves learning with positive reinforcers but not learning with negative reinforcers [27•].

The situation in the striatum is different: reinforcement-dependent responses occur with both rewarding and aversive stimuli [28], and neurons can change non-reward response gains on the basis of reinforcement and context [29,30]. Striatal neurons are closer to having a saliency signal related to behavioral policy and can predict behavioral outcome [31], an attribute also of their target neurons in the pallidum [32]. Inputs from the thalamus could be responsible for some of these effects [33•]. In the human striatum, positive and negative reward-prediction errors also elicit responses [34], and there is greater activation when reward delivery depends on the action

of the subject [35]. Thus, the saliency signal might be 'saliency for action'.

Taking account of regional differences will be crucially important for interpreting studies of the activity in the striatum and connected basal ganglia structures, which have representational topographies related to their cortical and thalamic inputs [36–38]. In human imaging studies, the ventral striatum (together with ventral insular cortex) exhibits greater activity for immediate rewards and dorsal striatum (and dorsal insular cortex) exhibits greater activity for future rewards [39]. Unpredictable reward can increase endogenous dopaminergic transmission in one part of the striatum and decrease dopaminergic transmission in other parts [40]. Remarkably, the caudate nucleus — dorsal striatum — appears to be selectively activated, along with a restricted number of limbic sites, under conditions evoking romantic or maternal love [41•,42] or, in two-person trust games, in relation to 'intention to trust' or 'altruistic punishment' [43•,44•]. The strong experience-dependent cognitive component of basal ganglia function must be included in models of how the basal ganglia promote optimum control.

Basal ganglia circuit anatomy and function: new challenges

How do these learning functions relate to the motor control functions long attributed to the basal ganglia? Much clinical and experimental work on the basal ganglia has been inspired by the idea that the basal ganglia can release or inhibit movement by the opposing influences of two main pathways originating in the striatum and extending through the pallidum and substantia nigra: the movement-releasing 'direct pathway' and the movement inhibiting 'indirect pathway'. These pathways, which have descending and ascending components, are accompanied by the 'striosomal pathway', which most strongly targets the substantia nigra and might be related to reinforcement. The cortical and thalamic inputs to these pathway neurons are excitatory, but there is an extensive network of inhibitory neurons in the striatum that can modulate its activity [45]. A powerful 'hyperdirect pathway' projects directly to the subthalamic nucleus from the motor cortex and other cortical areas and influences, if not controls, the output of the indirect pathway [46]. Many of the conventional views about these pathways are now open to revision (Figure 1).

Challenge 1: do the direct and indirect pathways project exclusively to different target nuclei?

Levesque and Parent [47••] report that in primates (squirrel monkey), the direct and indirect pathway axons have extensive collaterals that target all output nuclei of the basal ganglia (GPe, GPi, and SNr; globus pallidus external segment, globus pallidus internal segment, substantia nigra pars reticulata, respectively). They thus suggest that the direct and indirect pathways are not exclusively segregated as in the conventionally accepted direct (GPi, SNr) or indirect (GPe) pathways. In fact, they report a larger amount of collateralization in primates than that already reported for the rodent basal ganglia. What would this mean functionally? At the extreme, these findings could confound simple views of the direct and indirect pathways opposing each other to control movement selection and execution. There are other possibilities, however. The collaterals might not function or might function differentially. Another possibility is that copies of information in each of the pathways reach multiple basal ganglia output stations, and that other attributes of the pathways — related to impulse timing or to their different peptide contents, for example — are the critical differentiators of pathway operation. There is clearly a major need to develop methods to record from identified direct and indirect pathway cells of origin in the striatum in behaving animals.

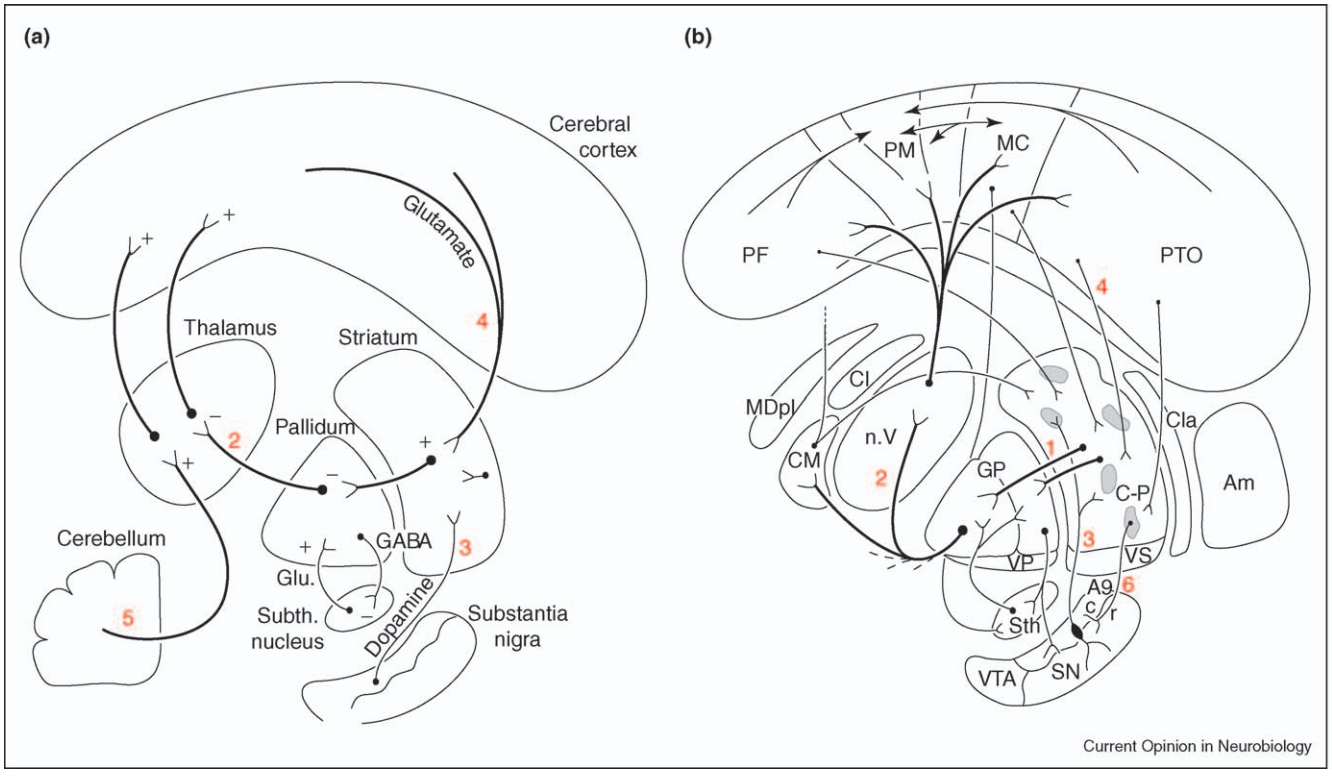
Challenge 2: is the pallido–thalamic pathway only inhibitory?

The 'double inhibitory pathway' setup of basal ganglia pathways has led to the well-known view that the basal ganglia enable the release of movement via the direct pathway: the cortex phasically excites direct path neurons in the striatum that phasically inhibit GPi, which itself otherwise would tonically inhibit the thalamus by its GABAergic innervation of the thalamic neurons. Person and Perkel [48••] now show that in the corresponding basal ganglia-to-thalamus pathway in the bird (zebra finch), the GABAergic input to thalamic neurons, produces not only inhibitory postsynaptic potentials (IPSPs) in the thalamic neurons, but also rebound spikes that have highly selective timing that is dependent on the frequency and patterning of the GABAergic inputs. This rebound excitation of thalamic neurons might function to carry a temporal code. More generally, these findings challenge the notion that basal ganglia outputs to the thalamus are only inhibitory.

Challenge 3: is dopamine the only neurotransmitter substance released by the dopamine-containing neurons of the midbrain?

Dopamine–glutamate interactions are at the heart of many ideas about information processing in the basal ganglia (and in the neocortex, where the dopamine-containing innervation is also considerable). Dopamine released in the basal ganglia comes nearly entirely from the dopamine-synthesizing neurons of the midbrain A8–A10 cell groups: the substantia nigra pars compacta (SNpc) and the ventral tegmental area (VTA). These neurons are thought to shape striatal responses to the massive glutamatergic inputs that come from the cerebral cortex and thalamus. Chuhma *et al.* [49••] now present evidence suggesting that the dopamine-containing neurons of the VTA produce fast excitation of nucleus accumbens (ventral striatal) neurons by releasing gluta-

Figure 1



Basal ganglia circuit anatomy and function: new challenges. **(a)** A sketch of motor control pathways involving the basal ganglia and cerebellum. **(b)** A diagram of cortico–basal ganglia circuits (omitting descending connections and many details) to illustrate the pathways highlighted in the text that are now being challenged by new experimental evidence. The numbers in red refer to the six challenges discussed in the text. Abbreviations: A9, cell group A9; Am, amygdala; c, pars compacta of substantia nigra; Cl, nucleus centralis lateralis of thalamus; Cla, claustrum; CM, centre median nucleus of thalamus; C-P caudate nucleus-putamen; Glu, glutamate; GP, globus pallidus; MC, motor cortex; MDpl, pars lateralis of thalamic mediodorsal nucleus; n. V, ventral nuclear complex of thalamus; PF, prefrontal cortex; PM, premotor cortex; PTO, parieto-temporo-occipital cortex; r, pars compacta of substantia nigra; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; Sth, subthalamic nucleus; VP, ventral pallidum; VS, ventral striatum; VTA, ventral tegmental area.

mate. They propose that glutamate released from the dopamine-containing neurons pushes the striatal neurons into an upstate (in which they can generate spikes in response to inputs), and that the dopamine released by these dopamine-containing neurons in response to burst firing determines how long the neurons will remain upstate. If confirmed and extended to the nigrostriatal system, this finding would fundamentally alter the way we think about dopamine–glutamate interactions in these systems. The convincingly demonstrated large dopaminergic input to the primate thalamus, from a range of dopamine-containing cell groups, further suggests that there are changes in store for work on the effects of dopamine on brain and behavior [50•]. Simultaneous, on-line recording of dopamine release and spike activity is a highly promising approach to this issue [51•].

Challenge 4: do the direct and indirect pathways receive equivalent information from cortical afferents?

It had long been assumed that any particular region of the neocortex, for example, the motor cortex, sends the same cortical information to striatal projection neurons whether they belong to the direct pathway or to the indirect pathway. But now, supporting earlier studies that seriously called this view into question, Reiner and coworkers [52••] demonstrate that collaterals of pyramidal tract neurons (PT neurons) project to indirect pathway neurons in the sensorimotor striatum, whereas direct pathway striatal neurons receive inputs from broadly distributed *en passant* terminals from non-PT pyramidal neurons that have intra-telencephalic projections (IT neurons). This finding might account for the remarkably selective activation of early genes in indirect pathway neurons by stimulation of the cortex [53]. The important functional implication is that indirect path striatal neurons could receive a corollary discharge (efference copy) of descending motor commands, whereas direct path neurons could receive a signal integrated with transcortical signaling. Notably, the putative corollary discharge inputs are in large terminals arranged in matrisome-like clusters, whereas the putative associative inputs are small and widespread. This could mean that

focal matrisomes process copies of motor commands to generate (or to terminate) the next movement in a sequence, with the context for that movement being represented more globally. Large post-movement responses do, in fact, occur in the striatum during movement [12•,54]. The hyperdirect motor cortex-to-subthalamic nucleus pathway could add to such corollary discharge processing [46].

Challenge 5: do the basal ganglia and cerebellum have fully separate functions and pathways to the neocortex?

The basal ganglia and cerebellum are the two largest stations in the extrapyramidal motor system. Opinions have swung back and forth about whether these two systems directly interact, but most now accept that the basal ganglia and cerebellum are both anatomically and functionally distinct. For example, in the motor learning field, the cerebellum has been associated with supervised learning and the basal ganglia with reinforcement learning [55], the cerebellum has been credited with developing internal models of motor action space. Hoshi *et al.* [56••] now report results from trans-neuronal viral transport experiments demonstrating that the cerebellum has a strong disynaptic projection to the putamen by way of the thalamus, and that this pathway specifically targets indirect pathway neurons of the putamen. This result suggests that the functions of the cerebellum and basal ganglia are linked well before the level of the cortex, and suggests that, at least for the sensorimotor striatum, the linkage holds for the striatal neurons that receive input from PT-type motor cortical neurons [52••]. This combination of findings opens the exciting possibility that some motor control functions (e.g. [57]) might be shared by cerebellar and basal ganglia-based systems and that these might co-exist with functions that are specific to each system.

Challenge 6: do striosomes code reinforcement-related signals?

The striosomal pathway has been claimed to target directly the dopamine-containing neurons of the striatum and, therefore, is considered as a likely candidate to mediate a reward prediction signal in the dopamine-containing neurons [55]. However, Levesque and Parent challenge this view in their study in squirrel monkeys [47••]. They find elaborate column-like arrays of striatonigral terminations in the non-dopamine-containing nigral pars reticulata (SNr), not in the dopamine-containing pars compacta. These results, if confirmed, would suggest that the striosomal input would only affect the dopamine-containing neurons themselves by indirect interactions within the nigral complex, if at all. This issue is important to settle from the functional point of view, as the striosomal system has been suggested to be reward-sensitive [58], and to be an important component in basal ganglia-based control of repetitive behaviors [59,60].

Conclusions and future directions

Many issues remain to be resolved at the systems level if we are to understand the functions of the basal ganglia in motor control. What are the functions of any given cortico–basal ganglia circuit or cortico–basal ganglia–brainstem circuit? How are the learning-related functions of the basal ganglia integrated with their motor and cognitive control functions? How are these functions integrated with those of other brain systems? What is the function of the prominent oscillatory activity in the basal ganglia [54,61,62,63•]? And, of course, how are these manifold functions related to basal ganglia-based disorders? The view proposed here is that, ultimately, through their integration of reinforcement and action-related signaling, the basal ganglia are in a position to take part in optimal control of movement and cognition.

Acknowledgements

Work from our laboratory cited here was funded by the National Institutes of Mental Health (MH60379), the National Institute of Neurological Disorders and Stroke (NS25529 and NS38372) and the Office of Naval Research (N00014-02-1-0023).

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