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## Network-level neuroplasticity in cortico-basal ganglia pathways

Ann M. Graybiel\*

*Department of Brain and Cognitive Sciences, McGovern Institute for Brain Research, Massachusetts Institute of Technology,  
45 Carleton Street, E25-618, Cambridge, MA 02139, USA*

### Abstract

The striatum, the largest input nucleus of the basal ganglia, receives massive inputs from the neocortex and thalamus, and gives rise to the direct, indirect and striosomal pathways of the basal ganglia. Here, the view is developed that the striatum is a major site for adaptive plasticity in cortico-basal ganglia circuits, affecting in the normal state a broad range of behaviours. This plasticity can become a major source of maladaptive responses in disease states affecting the basal ganglia.

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Establishing behavioural routines is central to normal human behaviour, and the capacity to build and to adjust such routines is critical for survival across the animal kingdom. Much evidence suggests that the striatum is part of the habit-forming system of the mammalian brain, and that abnormal activation of striatal circuits occurs in disorders ranging from obsessive–compulsive (OC) disorder to addiction [1–4]. A loss of automatic movements in Parkinson's patients, and their difficulty in performing highly practical tasks, or more than one task at a time, may also reflect a functional deficit in this system. More speculative, but discussed, is the possibility that some of the involuntary movements in hyperkinetic disorders such as Huntington's disease and even dyskinetic movements in L-DOPA treated Parkinson's patients may represent fragments of motor routines no longer purposefully controlled and embedded in a behavioural grouping. Such aberrant triggering may also be instrumental in generating tics and mannerisms in Tourette syndrome and compulsive behaviours in OC disorder. In some OC-spectrum disorders, a linkage between repetitive cognitive patterns and repetitive action patterns is particularly clear. Exposure to drugs of addiction can also produce severe forms of compulsive behaviour. The commonalities across this wide range of disorders suggest that the neural mechanisms underlying these disorders may also be shared, at least in part.

Moreover, the neural mechanisms that are engaged in these disorders may, in the normal state, help to lay down

the useful habits of everyday life. This thesis drives our work. In our laboratory, we have developed two approaches to study the neurobiology of procedural learning and habit formation. First, we have initiated studies with chronically implanted microelectrode and tetrode arrays allowing ensemble recording as rodents and monkeys learn and perform simple procedural tasks [5,6]. This method has the advantage of allowing us to monitor the responses of neurons during the course of behavioural learning. Second, we have used early-response gene expression assays to identify neurons differentially activated by stimulation of cortico-basal ganglia circuits or by repeated exposure to drugs acting on the dopamine system.

In physiological experiments in rodents, we have used variations of a T-maze procedure in which auditory or tactile cues instruct the animal to turn right or left to receive reward at the end of one of the end arms of the maze. Thus the animal, over time, must learn to run the length of the maze and also learn to associate the conditional cues with the correct turning behaviour [5–8]. This design was chosen to mimic natural behaviours in which animals learn to use environmental cues to guide sequential behaviours. Recording in the sensorimotor striatum (the rodent equivalent of the putamen), we found that, at the start of the training, many neurons responded to one or more aspects of the task. However, the response properties of the neuronal populations recorded from day to day gradually changed as learning occurred. After the animals had reached the behavioural criterion for learning, as judged by their percent correct turns in the maze, new ensemble patterns

\* Corresponding author. Tel.: +1-617-253-5785; fax: +1-617-253-1599.  
E-mail address: [graybiel@mit.edu](mailto:graybiel@mit.edu) (A.M. Graybiel).

of task-related activity emerged in the recordings. The pattern that developed was one in which the predominant neural activity shifted away from the active run and turn events toward events at the beginning and end of the maze runs: when the start gate opened to let the animal begin to run, and as the animal approached the reward-baited goal arm. It is as though, through learning, the sensorimotor striatum built up a representation of the entire procedure by marking its beginning and end, while at the same time devoting fewer neurons to the individual intervening events [1,5,9].

It is likely that different striatal districts develop different patterns as a result of learning, emphasizing, for example, the conditional cues [10]. It also is likely that such large-scale striatal plasticity is representative of altered activity patterns occurring throughout cortico-striatal loop systems—not only reorganized activity within the striatum. The key point, however, is that the ensemble responses of striatal neurons are not fixed. They can be tuned as a result of procedural learning.

Such flexibility in responsiveness is probably a general property of the central neurons system, as it is of neural networks. It thus is in identifying the *patterns* of change characteristic of particular brain regions that we may gain insight into the functions of these regions—sites in the distributed networks of regions activated by particular tasks. The pattern apparent in our maze experiments, and now in the primate experiments, is one in which task boundaries are emphasized. We have found a similar pattern of differentially strong activity at task start and end in recordings in the dorsolateral prefrontal cortex and caudate nucleus of macaques highly trained on a sequential saccade [11]. Interestingly, we have suggested the hypothesis that one function of cortico-basal ganglia loops is to build experience-dependent representations of actions that ‘chunk’ the elements of the actions into releasable action units [1].

With our recordings methods in rodents, most of the neurons recorded have spike waveforms indicating that they are striatal projection neurons (i.e. output neurons). Subpopulations of such neurons give rise to the three major output pathways of the striatum: the direct pathway, the indirect pathway and the striosomal pathway. Techniques do not yet allow identification of these three neuronal subclasses in ensemble recordings, but our experiments do suggest that neurons leading into the major basal ganglia output pathways can be shaped through learning to acquire or to lose particular response properties in favour of others.

The projection neurons of the striatum make up over 90% of all striatal neurons. The remaining neurons make up highly distinctive classes of striatal interneuron that interact with the output neurons and link with each other [12]. These interneurons are crucial to sculpting the network properties of the striatum. We could not reliably record from large numbers of these neurons in the rodent experiments,

but we have in related experiments in macaque monkeys. We focused on the learning-related activity of the tonically active neurons of the striatum (called TANs). These correspond, almost certainly, to the cholinergic interneurons of the striatum [13]. The TANs are readily identifiable in the primate striatum by their slow but tonic firing. We used simple sensorimotor conditioning paradigms in which a particular sensory conditioning cue (either auditory or visual) was paired with either a liquid reward or a mildly aversive air puff directed towards the side of the face. The monkeys learned either to lick when the conditioning cue came on in order to receive the reward, or to blink when the conditioning cue came on in order to avoid the air puff. During the course of the experimental training, the monkeys learned to respond to the conditional cues, and we recorded from the activity of single TANs in daily acute recording experiments [14–17].

The responses of these striatal interneurons were altered dramatically as a result of learning. Moreover, these changes could be reversed by extinction training and then reinstated by further training [14,17]. Interestingly, TANs recorded at distant sites in the striatum tended to exhibit similar, time-locked responses to the cues. These neurons, in fact, can exhibit synchronous responses [18,19].

The implication of these findings is that, as a result of learning, the intrinsic network properties of the striatum can be altered. The cholinergic interneurons of the striatum are known to project both to striatal output neurons and to other interneurons. This connectivity suggests that the TANs/cholinergic interneurons could influence the learning-related changes of the output neurons [20]. Supporting this view is the finding by the Nakanishi group that ablation of the cholinergic interneurons of the striatum produces a learning deficit in a maze task modelled on the maze task we used in recording during learning [21]. Moreover, we have found that toxin-mediated ablation of the cholinergic interneurons can block the reorganization of striatal neuron activity induced by repeated exposure to dopaminergic agonist drugs [22].

One of the targets of the cholinergic interneurons/TANs is the set of parvalbumin-containing interneurons in the striatum. These interneurons are able to generate widespread inhibition of striatal output neurons [23,24]. They receive strong excitatory input from the neocortex, and so they are the basis of powerful corticostriatal feed-forward inhibitory pathways influencing the output of the striatum. In the tetrode recording experiments in rodents, we have found strong task-related activity in fast-firing neurons that could correspond to these interneurons [6].

Experiments using early-gene expression as an identifier of activated neurons point to an important possible circuit-level function for these interneurons. This work is based on our finding, in experiments in monkeys, that cortical inputs to the striatum are organized so that a single small (e.g. 1 mm wide) site in the neocortex can project to dispersed modular domains within a given functional region (for example, the sensorimotor putamen)

[25–27]. With early-gene assays, we found that electrical stimulation at such a small cortical site (for example, at the foot representation in sensorimotor cortex) activates clusters of output neurons in the putamen at the sites of the clustered input-fiber modules [43]. Thus, input-output modules may organize cortico-basal ganglia circuits. Remarkably, cortical stimulation not only activates these modules (called *matrisomes*), but also activates parvalbumin-containing interneurons over the broad region containing the activated output-neuron modules. This pattern of activation suggests that the parvalbumin-containing neurons—which likely correspond to the fast-firing inhibitory interneurons—might function to focus striatal input-output processing. According to this proposal, these striatal interneurons could differentially suppress output neurons surrounding the activated modules, accentuating the differential activity of the activated foci [27]. At a functional level this modulation could lead to focal movement patterning by the striatal network, and even to focal dyskinesias or dystonias in abnormal states [28,29].

What evidence is there for such focal activity? Focal zones of task-related activity have been observed in the striatum with electrophysiological methods, [5,30–40] and such focal zones have also been found in experiments in rodents using the two deoxyglucose method as a metabolic marker for activity [41]. In macaque monkeys, we have recently observed focal zones of task-related activity in the oculomotor zone of the striatum as the monkeys performed saccade tasks [42]. We found that such focal zones could fall out of the otherwise highly synchronous pattern of 15–25 Hz local field potential oscillations, just at the time of the saccades. These findings suggest that there is general rhythmic activity in cortico-striatal pathways in the resting state, but when a particular movement is enacted, focal sites in the striatum can pop out of synchrony and take on individually specific patterns of activity. It seems likely that interneuronal circuits of the striatum contribute to this phenomenon, but there are no firm data yet available to test this idea.

Three general points emerge from the experiments reviewed. The first is that corticostriatal circuits are dynamically tuned as a function of experience. We suggest that this modifiability may directly contribute to the formation of behavioural routines. Second, this plasticity affects not only striatal projection neurons, but also striatal interneurons. It is likely that these striatal interneurons function to reconfigure corticostriatal transmission by differentially adjusting the gains of corticostriatal synapses, and probably the gains of other synapses as well. Third, corticostriatal inputs are organized in focal arrays that favour modular patterning of striatal output neuron activation. It is likely that this modular input-output organization, subject to dynamic shaping by interneuronal networks in the striatum, forms a template for the action-selection functions of cortico-basal ganglia circuits.

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