

# Basal ganglia — possible role in motor coordination and learning

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The basal ganglia, with their inhibitory efferents, control motor outputs either directly by their projections to the midbrain motor regions or indirectly through the thalamic nuclei. Neural mechanisms in the basal ganglia act selectively to remove or enhance the inhibition so that different combinations of motor signals, which may act as neural templates for motor learning, are formed.

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## Introduction

The phylogenetic development of the central nervous system has been achieved mainly by the addition of the cerebral cortices which have led to a newly acquired behavioral repertory. With this expansion, our perceptual as well as behavioral environment became enormously enriched and the need arose for selective control. Such a mechanism, however, could not be formulated by any simple combination of excitatory connections. Inhibition would seem to be the most fundamental and perhaps most efficient means of selection. The basal ganglia system is characterized by its inhibitory influences on target neurons. This contrasts with most other brain structures which send out excitatory signals. The basal ganglia could therefore play a general role in selection. For the selection to occur, however, at least two seemingly antagonistic features would have to be implemented. First, the basal ganglia would need to be composed of functional elements selectively related to individual components of behavior, whether innate or learned. Second, a neural mechanism would need to be present in the basal ganglia that would allow organization and reorganization of the functionally segregated elements to yield a new combination of movements.

Recent studies on the function of the basal ganglia, which range from molecular biological to human clinical studies, have provided evidence that the basal ganglia system is fine-tuned for behavioral selection while at the same time being flexible enough to produce new organizations of behavior. Because of this adaptability, the basal ganglia may possibly contribute to the formation of motor memory. This article is based on a wide range (but selected set) of experimental data and the ideas put forward here owe much to previous theoretical considerations. The hy-

pothetical function of motor learning is especially speculative and awaits future experimental studies.

## The basal ganglia contribute to the initiation of movement through disinhibition

How does the brain select a group of motor acts and arrange them in the spatial and temporal domains? This is a fundamental question for voluntary motor control. A possible mechanism for the selection would be to have both excitatory and inhibitory drives for each motor component, and then remove the inhibition of selected motor acts. The basal ganglia are in a good position to play such a role. The two major outputs of the basal ganglia, via the internal segment of the globus pallidus (GPI) and the substantia nigra pars reticulata (SNr), are mediated by  $\gamma$ -aminobutyric acid (GABA) and their activity levels are set extremely high due to their tonic background discharges. Major inputs to the GPI and SNr originate in the striatum, putamen and caudate nucleus (CD), which are also GABAergic and inhibitory. Thus, one mode of basal ganglia operation could involve an excitatory input (presumably glutamatergic) from the cerebral cortex or the thalamus that would lead to a disinhibition in the target structures of the basal ganglia. This scheme has been demonstrated for the saccadic oculomotor function in the monkey that is mediated by the CD and SNr, and whose target is the superior colliculus (SC) [1,2]. Chemical activation of CD neurons in the rat leads to suppression of the SNr-sustained discharge and eventually activation of SC neurons [3], as well as neurons in the thalamus [4]. These observations have led to the conclusion that the basal ganglia contribute to the initiation of movement through the mechanism of disinhibition [5]. An equivalent neural mechanism, the putamen–GPI–thalamus connection, may

### Abbreviations

CD—caudate nucleus; GPe—globus pallidus external segment; GPI—globus pallidus internal segment; MPTP—1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PPN—pedunculo-pontine nucleus; SC—superior colliculus; SNC—substantia nigra pars compacta; SNr—substantia nigra pars reticulata; STN—subthalamic nucleus.

well participate in the initiation of other types of movement.

### Brainstem control of the basal ganglia: a revival of the extrapyramidal system

Microstimulation of the CD in the cat induces coordinated movements of the eye and the head to the contralateral side [6]. The CD-SNr-SC connection is responsible for these synergistic movements. In addition to the SC, the basal ganglia have efferent connections with the brainstem, and may thus be able to control movements without having to access the cerebral cortex. A well known example of such a connection is to the pedunculopontine nucleus (PPN) which may have a prominent role in locomotion. Chemical blockade of GABAergic outputs from the SNr (by injection of muscimol) induces continuous locomotion in the cat [7], whereas the same procedure in the monkey leads to continual forced saccades [8]. Stimulation of the SNr produces monosynaptic inhibitory postsynaptic potentials in PPN neurons [9,10]. The relationship of the PPN to the basal ganglia is unique in that it has reciprocal connections with the SNr, GPi, and the subthalamic nucleus (STN). The PPN might also be viewed as part of the reticular activating system, which is largely cholinergic and controls the basal ganglia nuclei and a large part of the thalamus [11].

Oral movements might also be controlled by brainstem projections of the basal ganglia. Injection of muscimol into the rat SNr increases feeding, which is abolished by lesions of the SC [12]. Rhythmic jaw movements are induced in the guinea pig by electrical and chemical activation of a localized area in the mesencephalic reticular formation [13]. These data, taken together, suggest that the basal ganglia might control oral movement via their projection to the midbrain center responsible for this movement. Vocalization might be another candidate for basal ganglia control. The midbrain periaqueductal gray in the monkey contains neurons that discharge selectively before vocalization [14]; the SNr has efferent connections to the periaqueductal gray. Although not mentioned in any of these studies, a relationship of the basal ganglia with vocalization would be an interesting possibility.

The above scheme for the basal ganglia, although highly speculative, might lead to a new picture of motor control mechanisms. In this scheme, the midbrain would contain an assembly of motor stations controlled by the basal ganglia. An animal might be able to walk, run, orient, feed, and vocalize without the cerebral cortex. It would be amazing how integrated such an animal might look.

### Suppression of movement by the basal ganglia; role of the subthalamic nucleus

As described above, an important mode of basal ganglia operation is disinhibition which contributes to the initiation of movements. For the disinhibition to work properly, however, the level of tonic inhibition must be set at an appropriate level. Furthermore, an active change of the

level of the inhibition would add another perspective to basal ganglia function; that is, suppression of movement. The STN is now thought to provide the output elements of the basal ganglia, the SNr and GPi, with an excitatory drive [15] and may thus be viewed as a mechanism for motor suppression. With this mechanism, the cerebral cortices can actively suppress movements through either direct connections to the STN or indirect connections via the striatum and the external segment of the globus pallidus (GPe) (see Fig. 1). One can therefore understand how lesions of the STN could produce involuntary movements (ballism) [16].

It is not yet clear whether neural signals conveyed by the STN neurons are actually used for suppression. An interesting speculation can be made concerning oculomotor signals in the STN, however. A major group of STN neurons show a sustained discharge while the animal is fixating a target and anticipating a reward (M Matsumura *et al.*, unpublished data). The STN signal would help hold the SNr cell activity high via the excitatory connections, keep SC cells suppressed, and therefore suppress saccadic eye movements.

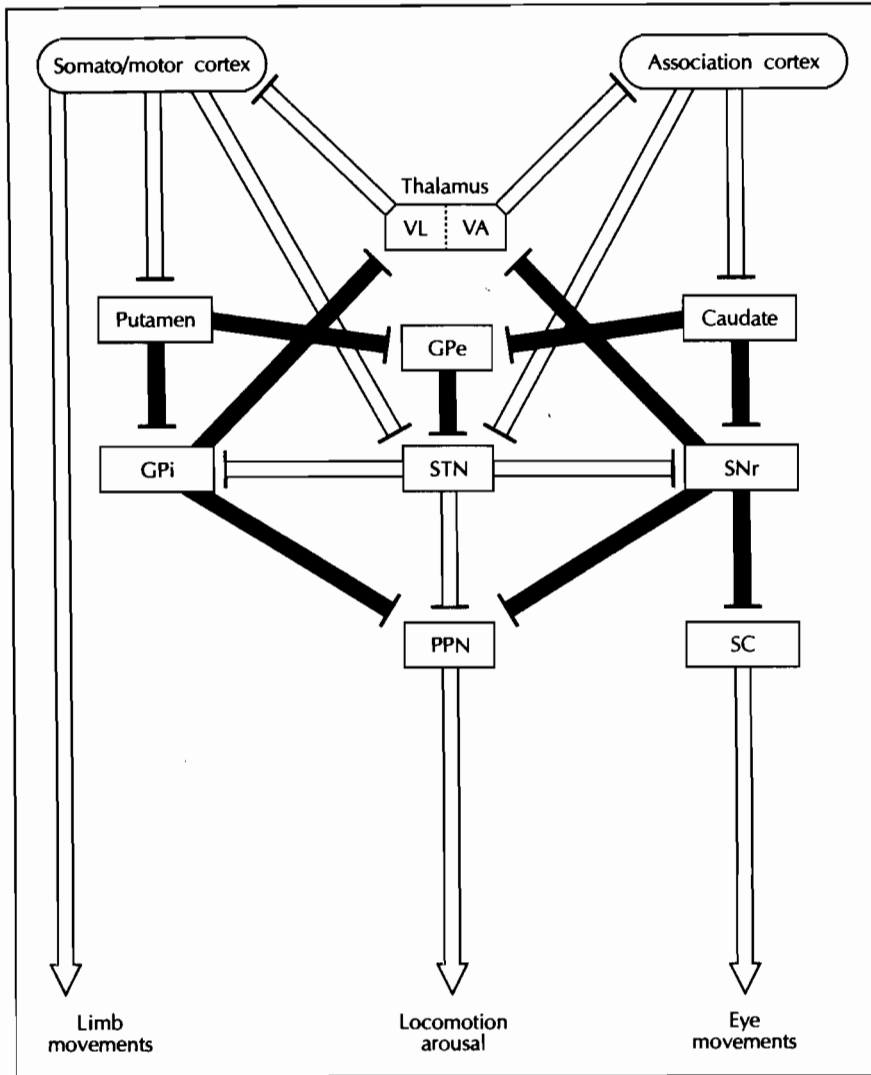
This example gives a further clue as to the role of the suppression mechanism. The saccade is suppressed not because it is irrelevant but because it is anticipated. In other words, preparation and suppression of a movement must go hand in hand. These two mechanisms are found to co-exist within the basal ganglia. If the system is in working order, it will use these mechanisms in an exchangeable manner so that a movement is initiated and terminated, or replaced by another movement. If not, the initiation, termination, and sequencing of movements would be devastated, as seen in parkinsonism.

### How do different motor signals interact in the basal ganglia?

Within the basal ganglia there is a functional segregation. The putamen, through its structural link with the somatosensory/motor cortices, performs skeletomotor functions, while the CD, through its link with association cortices, performs cognitive and oculomotor functions [17]. Somatotopy is present in the skeletomotor areas [18]. Neurotransmitter-specific patches (striosomes) and matrices in the striatum are another level of segregation [19,20]. Could segregation or classification therefore be the major tasks performed by the basal ganglia?

With our purposive behavior, different kinds of motor acts must be organized in a sequential as well as parallel manner. All of the motor acts and their sensory outcomes must be anticipated, consciously or subconsciously, at the outset of this behavior. Neural correlates for these motor acts must all be ready for activation, yet only some of them are activated at any one time. Selection must therefore come into play.

Figure 1, although oversimplified, is intended to clarify the concept that I would like to put forward. Without the GPe and STN, the skeletomotor and oculomotor/cognitive functions would be completely segre-



**Fig.1.** A simplified diagram to illustrate how different motor signals interact in the basal ganglia. The basal ganglia initiate (by disinhibition) or suppress (by enhanced inhibition) the innate repertory of movements through their access to the midbrain motor stations, superior colliculus (SC), pedunculo-pontine nucleus (PPN), etc. Learned limb movements are controlled by the basal ganglia through their access (via the thalamus) to the motor memory stored in the cerebral cortex. VL, ventrolateral thalamic nucleus. VA, ventroanterior thalamic nucleus. Different motor (and cognitive) signals remain segregated in the direct pathways, caudate–substantia nigra pars reticulata (SNr) and putamen–globus pallidus internal segment (GPi), but their spatio-temporal coordination can be achieved through indirect, antagonistic pathways via the globus pallidus external segment (GPe) and the subthalamic nucleus (STN). Selective modification of these pathways by slowly acting transmitters (e.g. dopamine) may underlie the motor coordination. The combination of motor signals created may act as a neural template for motor learning, which takes place in the premotor cortical areas. Note, this is a simplified diagram and the actual anatomical segregation is less clear (e.g. a part of the SNr receives inputs from the putamen, while a part of the GPi receives inputs from the caudate). The scheme represented here is intended to emphasize the conceptual framework of basal ganglia function. Black lines, inhibitory. White lines, excitatory.

gated, each contributing independently to the initiation of the respective function through disinhibition. Each of the systems could acquire a means of suppression if the GPe–STN collateral pathway is added. In this case, of course, the CD or putamen neurons projecting to the GPe would need to be selectively activated. As the CD–SNr and putamen–GPi systems share the same collateral system for suppression this is where interaction of the two systems might occur. If the CD neurons become generally active the signal might be conveyed in part through the CD–GPe–STN–GPi connection, thus activating GPi neurons. The reverse would also occur. In this situation, the oculomotor/cognitive function and the skeletomotor function would be antagonistic, an occurrence that may be common in everyday life. In a novel environment, oculomotor and mental searches may occur while hand movements are suppressed, but once the situation is comprehended hand movements would commence. Another way of generating suppression would be for the STN neurons to be activated directly; both the oculomotor/cognitive and skeletomotor functions would be suppressed, and locomotion possibly maintained. Yet another method would be to change the efficiency of

striatal neurons selectively depending on their transmitter subtypes [20,21]. For example, if GPe-projecting neurons in both the CD and putamen were selectively inhibited, the CD and putamen would become relatively free from the GPe–STN collateral suppression, and consequently eye and limb movements would occur simultaneously.

The assumption underlying the above arguments is that the GPe–STN system is shared by the CD–SNr system and the putamen–GPi system. This in fact may not be true. The putamen projects mainly to the ventral part of the GPe, while the CD projects to its dorsal part [22]. Skeletomotor neurons prevail in the dorsal part of the STN, while oculomotor neurons are clustered in its ventral part (M Matsumura *et al.*, unpublished data). The segregation is not absolute, however, and may be subject to changes according to the level and quality of motor learning. Interestingly, chemical blockade of the putamen by muscimol (a GABA agonist) leads to facilitation, and not suppression, of saccadic eye movements to the contralateral side (M Kato and O Hikosaka, unpublished data), supporting the idea of a common pathway.

Further support for a common pathway might be provided by pathophysiological data. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonian monkeys, GPI neurons show abnormally unselective responses to somatosensory stimulation [23], and to electrical stimulation of the CD and putamen [24]. It is possible that this may be due to the loss of the inhibitory effect of dopamine on GPe-projecting striatal neurons; the GPe-STN pathway would then dominate so that the GPI and SNr neurons would be overly and unselectively activated. This scheme has indeed been recently proposed to explain the disorders found in parkinsonism [25–29]. An interesting suggestion that has arisen from these data is that dopamine may play a critical role in the coordination (antagonistic suppression, coactivation, and general suppression) of different motor signals. Its action could be mediated by the differential activation of D<sub>1</sub> and D<sub>2</sub> receptors on striatal neurons [26,30••].

The above scheme may explain the motor dysfunction seen in human parkinsonism. The difficulty in performing two motor acts simultaneously is well known. Warabi *et al.* [31] have shown that when parkinsonian patients perform an eye-hand aiming task the hand movement tends to start after the eye movement is completed, not simultaneously as in normal subjects. A similar dysfunction is also seen for eye-head coordination [32].

### Basal ganglia may be instrumental in motor learning

When we learn a motor performance, we combine different motor acts in a particular combination and sequence. Every element of movement must be in our working memory, ready to be used, but tentatively suppressed. Sensory outcomes of the movement must also be embedded in the working memory so that the next movement can be prepared in a predictive manner. As motor learning proceeds, all these voluntary conscious stages will be replaced by a unitary behavior whose elements may be performed unconsciously.

Because the basal ganglia have antagonistic networks and a dopaminergic modulatory process, both of which are suitable for the selection and coordination of movement, it seems reasonable to assume that the basal ganglia also play a critical role in the active process of motor learning. Evidence supporting this idea has been provided by Schultz and Romo [33••,34]. Dopaminergic neurons in the substantia nigra pars compacta (SNc) are generally poorly-responsive to any sensory-motor manipulations, but when examined during the process of learning, these neurons show clear sensory responses which vary according to the type and level of learning.

The role of the basal ganglia in learning may not be limited to motor learning. From a comparison of a concurrent visual discrimination task with other memory tasks, Mishkin and Appenzeller [35] have put forward the hypothesis that visual memory and visuo-motor habits have different neural substrates, the former mediated by the limbic system and the latter by the striatum. A newly established pathway from the pre-

striate cortex and inferior temporal cortex to the tail of the CD and then down to the GPe, GPI, and SNr [36•] may well serve in the formation of habits. In MPTP-induced parkinsonian monkeys deficits in different types of learning are produced, but they are generally transient (N Miyashita and O Hikosaka, unpublished data).

I suggest that the basal ganglia play instrumental and possibly instructive roles during the formation of motor memory, but that motor memory itself is stored outside the basal ganglia, perhaps in the premotor cortical areas. Of course, this instrumental/instructive function is not independent of the gating/coordinative function described in the previous sections. Rather, they are two different aspects of basal ganglia function. The context-dependent nature of basal ganglia neuronal activity may be understood based on this framework. It may be selective or preferential for movements which are planned internally [37•], guided by memory [1,2], or triggered by sensory stimuli [2,38]. Sensory responses are common, but are usually dependent on the behavioral outcome predicted by the sensory stimulation [33••,34,39,40]. Even the responses correlated with prediction or expectation are commonly seen in the CD [41]. Preparatory and movement-related activity in the putamen may be selective for the direction of the target or the direction of movement, as seen in the motor and supplementary motor cortices [42••].

According to the mechanism proposed above, these seemingly arbitrary response combinations might be explained as follows. A given neuron in the basal ganglia may be potentially responsive to a wide variety of inputs [24], but because of the selection or switching mechanisms the neuron is rendered selective in its responsiveness. The selectivity could be determined by the state of behavioral experience or learning, and temporarily maintained until perhaps the relevant motor memory is formed in the premotor cortices. The neuronal responses are therefore task-dependent, most commonly related to the behavior that is currently being learned, and less commonly related to the behavior already learned. As long as the basal ganglia work in such an instrumental/instructive mode, the neuronal activity need not start early enough to act as a command [43]; of course, this does not preclude the possibility that the basal ganglia do work in a command mode.

The selectivity of movement deficits in human or experimentally induced basal ganglia disorders may reflect the instrumental/instructive function of the basal ganglia. The deficits in memory-guided saccades are more prominent than those in visually guided saccades [44–48], whereas the deficits in visually guided jaw movement are more prominent than those in jaw movements in natural speech [49]. A common finding in these situations is that the deficits are stronger for the type of movement that requires focusing of instruction.

### Conclusion

The basic mode of basal ganglia function involves the combination of tonic inhibition, exerted by the SNr and

GPI on target structures, and removal of this inhibition (disinhibition). The disinhibition is produced by another set of inhibitory pathways originating from the striatum (CD and putamen). Cortical, thalamic, limbic, and brainstem signals fed into the basal ganglia are used for the control of behavior either directly via projections to the midbrain motor regions or indirectly via projections to the thalamic nuclei. The midbrain projections would suppress (by enhancing the inhibition) or allow (by removing the inhibition) the innate repertory of movements (eye/head orientation, locomotion, oral movement, vocalization), while the thalamic projections would either withhold the ongoing thalamocortical activity or allow it to proceed based on the stored motor memory.

The basal ganglia system is equipped with both fine-tuned functional/structural elements and flexible selection mechanisms. Central to the selection mechanisms is a collateral system composed of the GPe and STN which could act on the final outputs of the basal ganglia (GPI and SNr) to enhance the inhibition that is antagonistic to the disinhibition. This collateral system is shared by different functional subsystems—for instance, the oculomotor/cognitive system (association cortex–CD–SNr) and the skeletomotor system (somatosensory/motor cortex–putamen–GPI)—thus providing a means for the selection. Different types of motor/cognitive activity could be activated or suppressed simultaneously, selectively, or sequentially, depending on which elements in the basal ganglia are activated. Furthermore, it is speculated that such a combination of neural activity may reflect the state of motor learning and perhaps act as a template for the spatio-temporal organization of behavior stored in the premotor/prefrontal cortical areas. Underlying the template formation could be a wide variety of slow-acting neurotransmitters. Dopamine, for example, might act differentially on GPI/SNr-projecting and GPe-projecting neurons in the striatum, thus contributing to the reorganization of the neural template.

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Basal ganglia are the oldest structure in your brain, coordinating movement, motivation, and reward for 560 million years. Learn more here. Unsurprisingly given their role in decision-making and working memory the basal ganglia also help you learn and build habits. By reinforcing behaviors with either good or bad feelings (reward or punishment), the basal ganglia help us figure out what to do in situations we've encountered before [8, 6]. The reinforcement can be disguised as anything from a social reaction (people frown or smile in response to your behavior), material goods (treats, toys, money), or specific events (injury, fear, pleasure, etc.). The basal ganglia also control curiosity and the desire (or lack thereof) for new e The basal ganglia and related nuclei are characterized as one of three types of nuclei. Input nuclei receive signals from various sources in the brain. Output nuclei send signals from the basal ganglia to the thalamus. The subthalamic nucleus plays a major role in voluntary and involuntary movement. It is also involved in associative learning and limbic functions. Subthalamic nuclei have connections with the limbic system through connections with the cingulate gyrus and nucleus accumbens. Substantia Nigra: This large mass of nuclei is located in the midbrain and is also a component of the brainstem. It is involved mainly in motor control and coordination. Pars compacta cells contain pigmented nerve cells that produce dopamine. basal ganglia: contribution to motor system. - basal ganglia and cerebellum = 2 parallel systems. BOTH: -- get copies of commands and regulate mov't -- send info back through thalamus, to the motor cortex, brainstem and SC -- receive input from and send output to cerebral cortex through separate parts of thalamus. basal ganglia: damage. >> too much or too little mov't - results in motor speech disorders --- 2 major types: hyperkinesia & hypokinesia. - fastigial nucleus = gross motor coordination and balance; sends information mainly to vestibular and reticular nuclei (kick a ball, throw a ball, walk, jump). peduncles.