

THE BASAL GANGLIA

That the basal ganglia are related to the control of movement has been known for a long time; diseases affecting primarily the basal ganglia lead to characteristic disturbances of movement and of resting muscle tone. Improved methods for tracing fiber connections have shown, however, that the main efferent connections of the basal ganglia do not descend to motor nuclei in the brain stem and spinal cord but are rather directed 'upstream' to the motor and other areas of the cerebral cortex. Even though the most obvious symptoms of the basal ganglia are related to the motor system, both clinical and experimental evidence indicates that the basal ganglia also play a role in higher mental functions.

STRUCTURE AND CONNECTIONS OF THE BASAL GANGLIA

Components: caudate nucleus + putamen = striatum; putamen + pallidum = nucleus lentiformis. putamen+caudate = neostriatum; pallidum = paleostriatum; Neostriatum + paleostriatum = corpus striatum. Other components: subthalamic nucleus; substantia nigra = pars compacta (SNc) + pars reticulata (SNr).

Afferent connections: The striatum, which is the primary receiving part of the basal ganglia, is characterized by three sets of afferents 1) from the cerebral cortex, 2) from the intralaminar thalamic nuclei and 3) the dopamine containing cell groups in the substantia nigra. The largest contingent of afferents comes from the cerebral cortex. Almost all areas of the cortex send fibers to the striatum, but the caudate nucleus and the putamen receive from different parts of the cortex. The putamen is dominated by somatotopically organized inputs from the SI and MI. The caudate nucleus, on the other hand, receives fibers predominantly from association areas.

Cell Types and Compartmental Organization of the Striatum.

More than 90% of the neurons have relatively small perikarya and dendrites with numerous spines (medium-sized spiny neurons}. This cell type contain GABA. There appear to exist two subtypes of this medium spiny neuron: one kind contains Substance P in addition to GABA and project primarily to the internal segment of the GP (or entopeduncular nucleus in rat) and SNr; the other contains enkephalin in addition to GABA and projects mainly to the external segment of the pallidum. Other cell types are interneurons containing acetylcholine, NPY, somatostatin. The various cell types, and in particular the neurotransmitters, are not evenly distributed throughout the striatum. Rather, different smaller compartments can be defined with regard to connections and cytochemistry. In microscopic sections, a mosaic pattern appears after staining to demonstrate acetylcholine esterase. Poorly stained patches called striosomes are embedded in a heavily stained matrix.

Several neuropeptides such as substance B, somatostatin, and enkephalin, are most abundant within the striosomes. GABAergic projection neurons are found within both compartments. The connections of the striosomes and the matrix compartments also differ, for example, neurons in the deep parts of LV of the frontal cortex provide inputs to the striatal patch compartment, whereas superficial LV neurons provide inputs the striatal matrix. Patch neurons provide inputs to location of dopaminergic neurons in the SNC. Striatal matrix neurons provide inputs to GABAergic neurons in SNr.

Paralell Circuits, Linking Cortex, Basal Ganglia and Thalamus

The effects exerted by the basal ganglia on other parts of the nervous system are mediated primarily by efferent fibers from the pallidum and substantia nigra. These nuclei receive their main efferents from the striatum. The efferents from the internal pallidal segment goes to the thalamus (VA,VL, and CM), while the external pallidal segment project to the subthalamic nucleus, which in turn project to the substantia nigra pars reticulata. In addition, the external pallidum also projects directly to SNr. The SNr send fibers to the superior colliculus, thalamus and the mesopontine tegmentum. The parts of the thalamus that receive fibers from the pallidum and the nigra project back to different portions of the frontal lobe.

Earlier schemes suggested that projections from diverse cortical areas including motor, sensory, and "association" fields, converged within the basal ganglia and were then funneled back upon precentral motor

areas. Currently, however, the weight of evidence suggests a different type of organization: the basal ganglia, along with their connected cortical and thalamic areas, are viewed as components of parallel circuits whose functional and morphological segregation is rather strictly maintained. Each circuit is thought to engage separate regions of the basal ganglia and thalamus, and the output of each appears to be centered on a different type of the frontal lobe: the "motor" circuit is focused on the precentral motor fields; the "oculomotor" circuit on the frontal eye fields; the "prefrontal" circuits on dorsolateral prefrontal and lateral orbitofrontal cortex; and the "limbic" circuit on anterior cingulate and medial orbitofrontal cortex.

Each circuit contains a number of highly specialized channels and sub-channels that permit parallel, multilevel processing of a vast number of variables to process concurrently. Within the "motor" circuit for example, a well defined somatotopy is maintained throughout all stages of the circuit, thereby giving rise to clearly differentiated "leg", "arm" and "orofacial" channels. There is also evidence suggesting further subdivisions of the "motor" circuit in terms of a) the types of behaviors observed (movement preparation vs. execution) and b) the maintained segregation of influences from different cortical areas (e.g. separate subchannels for each of the precentral motor fields). Moreover, included within each of the basal ganglia thalamocortical circuit is a direct pathway that passes from the striatum directly to one of the basal ganglia output nuclei, and an "indirect" pathway which includes a relay through the external pallidum and subthalamic nucleus. In addition, within each of the somatotopic channels of the motor circuit (leg, arm, orofacial) there may be another level of organization comprising functionally specific sub-channels that encode selectively, but in parallel, information about such disparate motor behavioral variables as target location, limb kinematics (direction of limb movement) and muscle pattern. Activity within these circuits initiated in the cortex, although there is an essentially complex temporal overlap, suggesting that much of the motor processing proceeds concurrently and functional integration is based upon temporal coincidence of processing within pathways whose functional separation is rather strict.

The oculomotor circuit The frontal eye fields and several other cortical areas project to the body of the caudate. The caudate then projects to both the superior colliculus and the frontal eye field via the thalamus. The circuit is involved in the saccadic eye movement. The dorsolateral orbitofrontal circuit The dorsolateral prefrontal cortex and several other areas of association cortex project to dorsolateral head of caudate which in turn project back to the dorsolateral prefrontal cortex via the thalamus. This circuit is probably involved in aspects of memory concerned with orientation in space. The lateral orbitofrontal circuit through the ventromedial caudate and thalamic MD nucleus is thought to be involved in the ability to switch behavioral set. The limbic circuit involves the anterior cingulate area (ACA)-medial orbitofrontal cortex (MOFC)-ventral striatum-ventral-pallidum-MD projections. This circuit is closed by thalamocortical projections from MD thalamus to ACA and MOFC. The limbic circuit may play some role in emotional and/or motivational processes.

Operational Features of Basal Ganglia-Thalamocortical Circuits

Physiological activity in the two striatal output pathways differentially modulate the GABAergic neurons in the SNr. At rest, striatal output neurons are physiologically quiescent, whereas nigral GABAergic neurons are tonically active. Corticostriatal inputs stimulate activity in striatonigral neurons which phasically inhibit the tonic activity of nigral GABAergic neurons, thus disinhibiting the VL thalamus and thereby gating or facilitating cortically initiated movements via excitatory thalamocortical connections. Cortically driven activity of striatopallidal neurons inhibits external pallidal GABAergic neurons, resulting in the disinhibition of the subthalamic nucleus, which increases the tonic firing of nigral GABAergic neurons. Phasic increases in GPi/SNr discharge increases the inhibition in the superior colliculus or thalamic target nuclei. The execution of a movement requires temporal coincidence of basal ganglia disinhibition with command signals from other sources so that the disinhibitory process is based on a gating effect. The function of the arousing striatal disinhibition is to set a pattern of readiness in premotor network that will be further activated for the execution of movement.

The Action of Dopamine in the Striatum is Complex

The relative responsiveness of striatonigral and striatopallidal neurons to cortical input determines the pattern of activity of the output neurons of the basal ganglia. As determined by *in situ* hybridization histochemistry, striatopallidal GABAergic neurons express enkephalin and D2 dopamine receptor, whereas the majority of striatonigral GABAergic neurons express substance P, dynorphin (Dyn) and D1 dopamine receptor. Dopamine depletion in the striatum results in increased ENK mRNA expression in striatopallidal neurons and decreased expression of Dyn and substance P mRNA in striatonigral neurons. Subsequent to dopamine depleting lesions, D1 or D2 selective agonist treatments reverse the lesion-induced changes (see Gerfen's Fig.). The increases and decreases in gene expression in striatonigral and striatopallidal neurons parallel changes in the physiological activity of these neurons in similar experimental paradigms assayed by 2-deoxyglucose and in electrophysiological studies. These studies suggest that dopamine deafferentation produces an imbalance in the activity of striatopallidal (indirect) and striatonigral (direct) output pathways, which results in increased tonic activity of nigral output neurons through the polysynaptic circuits.

DISEASES OF THE BASAL GANGLIA

The most frequent disease affecting the basal ganglia is Parkinson's disease (PD). Typically, voluntary movements are hard to initiate (*akinesia*) and they are slower and smaller than normal (*bradykinesia*). The akinesia also leads to a conspicuous lack of facial movements (mask-like face). In addition, there is an increased muscular rigidity (rigidity results when agonist and antagonist muscles are activated simultaneously) and *resting tremor* (the tremor becomes quieter, if not entirely quiescent, once the patient initiates a volitional movement). When the limb is displaced passively, the neurologist can feel alternations between resistance and relaxation, a phenomenon known as cogwheeling. Patients with Parkinson's disease have a pronounced cell loss in the SNc and a corresponding decrease of dopamine in the striatum. Akinesia, the dominant symptom in PD, has been related to increased striatopallidal activity (through activating D2 receptors in ENK/GABA striatopallidal neurons) and the resultant increase in excitatory subthalamic inputs to nigral GABAergic neurons, which then predominate over the disinhibitory mechanisms required for the generation of movements. This model is supported by the report that lesions of the subthalamic nucleus reverse akinesia in monkeys made Parkinsonian with lesions induced by MPTP. To alleviate the symptoms, L-dopa, the precursor of dopamine, is used. The L-dopa treatment, however, has side effects. Especially, long-term treatment may provoke motor symptoms that are different from those caused by the disease, such as chorea-like and athetoid dyskinesias. The mechanisms of these dyskinesias may be the same as proposed for the one in Huntington's disease and hemiballism.

In Huntington's disease, in which there is a marked loss of GABAergic neurons of the striatum, the most pronounced symptom is involuntary, jerky, often dance-like movement (chorea). Apparently, the cell loss in the striatum mainly concerns the neurons projecting to the external pallidal segment (*GABA/ENK/D2*), whereas the loss of neurons projecting to the internal pallidal segment (containing *GABA/SP/D1*) occurs at a later stage. Accordingly, the loss of striatopallidal GABAergic neurons leads to increased activity of inhibitory pallido-subthalamic neurons. The reduced activity of the subthalamo-nigral projection then leads to reduced inhibition of the nigro-thalamic neurons, which finally results in increased thalamocortical activity. Another hypothesis focuses on the possible hyperactivity of dopaminergic nigrostriatal neurons, which are normally inhibited by GABAergic striatonigral neurons. This is consistent with the experience that antidopaminergic therapies tend to reduce the choreiform movements.

The basic pathophysiologic mechanism suggested for the generation of involuntary movements in Huntington's disease may also be involved in a rare disorder known as hemiballismus, which is usually caused by a vascular lesion in the subthalamic nucleus. In this instance, the loss of excitatory subthalamic input to basal ganglia output structures results in disinhibition of their targets, which results in suddenly developing symptoms of violent flinging movements of the extremities contralateral to the lesion.

DISEASES AS LESIONS OF THE CORTICO-STRIATO-PALLIDO-THALAMIC CIRCUITRIES

The concept of parallel circuits also explains why often the same symptoms can be observed caused by lesions at different locations in the fronto-striato-pallido-thalamocortical loop. In other words, behavioral syndromes observed with frontal lobe lesions are recapitulated with striatal or thalamic lesions and there are recognizable circuit-specific behaviors.

Huntington Disease. Patients with HD manifest deficits on the Wisconsin Card Sort Test (WCST), decreased verbal fluency, poor recall of recently learned information similar to dorsolateral prefrontal dysfunction. HD patients had mood disorders (37%), irritability (30%) and antisocial personality (6%). Thus, in HD, cognitive and behavioral alterations corresponding to dysfunctions of all three behaviorally relevant fronto-caudate circuit projections are evident. The early appearance of personality alterations in HD corresponds to the involvement of medial caudate regions receiving projections from the orbitofrontal and anterior cingulate circuits. The cognitive deficits in HD reflect involvement of the head of the caudate receiving lateral prefrontal projections.

Dorsal caudate lesions produce executive function deficits (impaired performance on the WCST), ventral caudate lesions are associated with disinhibition and inappropriate behavior, and acumbens lesions produce apathy and lack of initiative.

Globus pallidus lesions. Three discrete syndromes equivalent to the frontal lobe symptom complexes cannot be identified in patients with GP lesions. Nevertheless, mixture of apathy, irritability and neuropsychological deficits affecting memory and executive functions resembling those of patients with frontal lobe lesions are present. Given the progressive spatial restriction of the parallel circuits at this anatomical level, focal lesions may involve several circuits simultaneously, resulting in mixed behavioral syndromes.

Thalamic syndromes. Vascular and degenerative disorders affecting the thalamus reveal that typical frontal lobe type behaviors can be observed with lesions of the thalamus. With bilateral paramedian thalamic infarction, the patients were dysphoric, irritable, one alternated between fretfulness and silly cheerfulness, and one was disinhibited and inappropriate. The patients had memory deficits (Gentilini). Patients with bilateral medial thalamic infarction showed disinhibition, apathetic irritability, utilization behavior and distractibility. Neurobehavioral examination revealed decreased mental control, poor memory and reduced verbal fluency. Poor performance with WCST (Eslinger).

FUNCTION OF BASAL GANGLIA (BG) AS SWITCHING BETWEEN ACTIONS

According to this notion the BG perform an operation critical for shifting mental set. In the motor domain, a problem in initiating movements can be viewed as a deficit in set shifting. The Parkinsonian patient gets stuck in one position or posture and cannot shift to a new one. The BG is in a position to monitor activation across wide regions of the cortex, allowing a shift between different actions and mental sets by removing an inhibitory influence in selected neurons. In one experiment (Brotchie et al, 1991), monkeys were trained to make a pair of movements with a variable delay between the first and second movements. A burst in pallid neurons observed at the end of the delay period was interpreted as a releasing signal for the cortex to switch from one plan to another.

This shifting hypothesis also may hold the key to the basal ganglia's role in learning. Dopamine is known to play a critical role in reward system of the brain, providing the organism with neurochemical marker of the reinforcement contingencies that exist for different responses in the context of the current environment. Learning involves change in behavior –either acquiring the appropriate response in an unfamiliar context or breaking a habitual response when contingencies change in a familiar context. For a rat in the wild, this might mean being sensitive to a change in the availability of food at a foraging site. For a human, it might mean

recognizing that a demanding problem cannot be solved by conventional means. One can hypothesize that within the BG, dopamine serves to bias the system to produce certain responses over others. Dopamine release in the striatum follows successful actions. This transmitter may modify the input-output channels in the BG, making it more likely that the animal will shift to the previously rewarded action when the associated input pattern is reactivated in the future.

Viewed this way, the ability to shift is required for producing novel behavior or for combining patterns of behavior into novel sequences. A cardinal feature of Tourette's syndrome (TS) and OCD is the repetitive production of stereotyped movement patterns. For the patient with TS, this might be a simple tic, or a hand brushing across the face; with OCD, an entire behavioral sequence, such as hand washing can be performed over and over again. A failure to shift may result in an absence of movement, the problem of the PD patient, or in the repeated production of a single pattern.