

Circuits and Circuit Disorders of the Basal Ganglia

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Views of the anatomy and function of the basal ganglia and their role in motor and non-motor disorders have undergone major revisions during the past decades. The basal ganglia are now appreciated as components of parallel, reentrant cortico-subcortical circuits, which originate from individual cortical areas, traverse the basal ganglia and thalamus, and terminate in their respective areas of origin in the frontal lobe. Further research and clinical experience have resulted in new insights and perspectives on the details of the circuitry and on the role of these structures in Parkinson disease and other basal ganglia disorders. On the basis of anatomical and physiological studies and the striking success of focused surgical interventions, it seems appropriate to view these varied clinical disorders as circuit disorders, resulting from pathologic disturbances in neuronal activity throughout specific cortico-subcortical loops.

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BASAL GANGLIA CIRCUITS

In the 1970s, the basal ganglia were believed to integrate projections from diverse portions of the cortex and project this information, via the thalamus, to the motor cortex and supplementary motor area. This scheme provided a mechanism by which movement initiation could originate from diverse functional cortical areas. More recent neurophysiological and anatomical studies have suggested, however, that input to the basal ganglia from different cortical areas terminates within specific basal ganglia territories, which are connected to similarly specific portions of the thalamus. These thalamic areas, in turn, project back to the same areas of the cortex from which the circuit originates.¹⁻³

These segregated reentrant loops are able to influence widespread areas of the frontal lobe and play a role in far more than simply motor functions. The different circuits were designated based on the pre-

sumed functions of the cortical areas from which they originate, including motor, oculomotor, prefrontal associative, and limbic areas. The segregated organization of these loops has recently been given further support by studies using retrogradely transported virus particles.³ These studies have also resulted in the identification of 2 additional circuits and a detailed description of segregated subcircuits that make up the larger circuits (see the **Figure** for an example of the structures involved in forming the motor circuit). Although some uncertainty remains regarding the degree of segregation between circuits and whether the circuits are truly closed or partially open, the overall scheme has been accepted by most researchers and has provided a framework for understanding the diverse behavioral disturbances clinically evident in disorders of the basal ganglia and a rational basis for new surgical treatments for some of these disorders.

In addition to the topographic organization of the cortico-subcortical loops, additional details of the anatomy of the intrinsic and extrinsic connections of the

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basal ganglia have been worked out (Figure). The striatum and the subthalamic nucleus (STN) receive topographically organized input from the cerebral cortex, whereas the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) provide basal ganglia output to the thalamus and brainstem. The connections between the striatum and these output structures are organized into a monosynaptic inhibitory (γ -aminobutyric acid [GABA]-ergic) direct pathway and a net excitatory polysynaptic indirect pathway that includes the external globus pallidus (GPe) and the STN. Striatal neurons that give rise to the direct and indirect pathways receive cortical input, potentially from different cortical source neurons. Additional input to the striatal direct pathway neurons comes from the intralaminar nuclei of the thalamus (ie, the centromedian and parafascicular nuclei). The GPi and SNr neurons give rise to GABAergic projections, which because of their high discharge rate tonically inhibit thalamocortical projection neurons in the ventral anterior, ventrolateral, and intralaminar nuclei of the thalamus, as well as brainstem neurons. Given the polarity of the connections involved, activation of striatal neurons that give rise to the direct pathway is thought to inhibit GPi and SNr, whereas activation of striatal neurons that give rise to the indirect pathway may exert a net excitatory effect on these output nuclei.

The most researched cortico-subcortical circuit is the “motor circuit” because of its importance for movement disorders. The motor circuit is composed of several subcircuits that originate from the motor cortex and several premotor areas (Figure). In a general sense, tonic output from this circuit, arising in motor portions of the GPi and SNr, may regulate the overall amount of movement. Increased basal ganglia output could translate into less movement through inhibition of thalamocortical projection neurons, whereas reduced basal ganglia output could translate into increased movement because of disinhibition of these neurons. Although no direct evidence is available, it has been proposed that the combined action of information traveling via the direct and indirect pathways may scale or focus movements.⁴ To achieve scaling of movement parameters or termination of movements, striatal output would initially inhibit specific neuronal populations in the GPi and SNr via the direct pathway, hence facilitating movement, followed by disinhibition of the same GPi and SNr neuron via input over the indirect pathway, thus inhibiting ongoing movement. In the alternative focusing model, inhibition of relevant pallidal and nigral neurons via the direct pathway would allow intended movements to proceed, whereas unintended movements would be suppressed by concomitant increased excitatory input to other GPi and SNr neurons via the indirect pathway.

The balance between direct and indirect pathways is regulated by the differential actions of dopamine on striatal neurons from terminals of neurons in the substantia nigra pars compacta. Release of dopamine in the striatum increases activity along the direct pathway (acting on D1 receptors in striatal neurons) and reduces activity along the indirect pathway (acting on D2 receptors). Together these actions result in a net reduction in GPi and SNr activity.

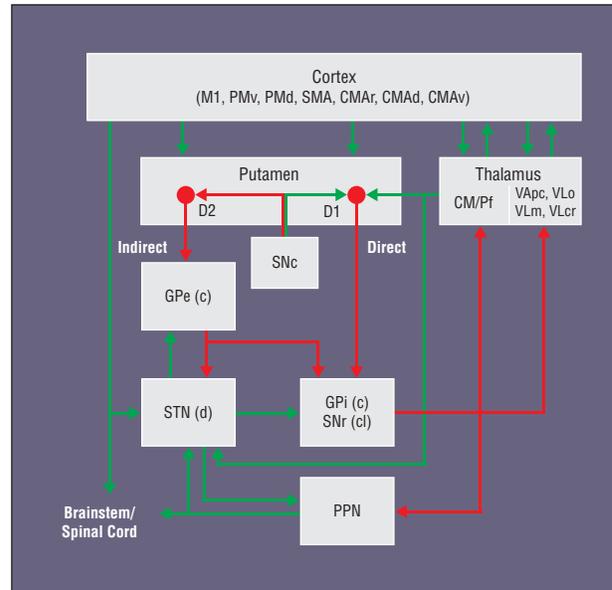


Figure. Intrinsic circuit anatomy of the motor circuit. The cortical motor areas give rise to a specific motor subcircuit. Red arrows indicate inhibitory (γ -aminobutyric acid [GABA]-ergic) connections; green arrows, excitatory (glutamatergic) connections. CM indicates centromedian nucleus of thalamus; CMAr, rostral portion of cingulate motor area; CMAv, ventral portion of cingulate motor area; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; M1, primary motor cortex; Pf, parafascicular nucleus of the thalamus; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PPN, pedunculopontine nucleus; SMA, supplementary motor area; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VApc, ventral anterior nucleus of thalamus pars parvocellularis; VLm, ventrolateral nucleus of thalamus pars medialis; VLo, ventrolateral nucleus of thalamus pars oralis; VLcr, ventrolateral nucleus of thalamus rostral pars caudalis; c, caudal; cl, caudolateral; and d, dorsal.

Conversely, a decrease in striatal dopamine release would result in an increase in GPi and SNr activity.

PARKINSONISM

Parkinsonism is a movement disorder characterized by the triad of bradykinesia, tremor at rest, and muscular rigidity, which results from a decreased dopaminergic tone in the motor portions of the putamen. In idiopathic Parkinson disease (PD), these motor features are often accompanied by nonmotor issues such as depression, anxiety, autonomic dysfunction, sleep disorders, and cognitive impairment, which are believed to result from a combination of dopamine deficiency in the nonmotor portions of the striatum and more widespread progressive pathologic changes in the brainstem, thalamus, and eventually the cerebral cortex.⁵ Little is known, however, about the consequences of extranigral neuronal degeneration in PD. Therefore, the following paragraphs focus on the motor aspects of PD that result from the loss of nigrostriatal dopamine.

Pathophysiological Models of Parkinsonism

The study of changes in motor circuit activity in PD has been greatly facilitated by the availability of the 1-methyl-

4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of the disease. Metabolic imaging and electrophysiological studies in the MPTP model have demonstrated that neuronal discharge is increased in the STN, GPi, and SNr but decreased in the GPe. These findings prompted the development of a model in which dopamine depletion leads to (1) increased activity of striatal indirect-pathway neurons, resulting in increased inhibition of GPe, disinhibition of STN, and subsequent increased excitation of GPi and SNr, and (2) decreased activity of striatal direct-pathway neurons. The net effect of dopamine loss is an increase in the inhibitory output from GPi and SNr and thus decreased activity in thalamocortical neurons.

Parkinsonism, according to this "rate model," results from excessive inhibition of components of the motor circuit in the thalamus, cortex, and brainstem. These aspects of the rate model are generally supported by lesioning and inactivation studies, which have shown that inactivation of the sensorimotor portions of the STN or GPi increases the metabolic activity in cortical motor areas and improves bradykinesia and tremor in patients with PD. The rate model also predicts that involuntary movements would result from reduced firing in the GPi. Recording studies have demonstrated that GPi activity is reduced in monkeys and in patients with PD who have ongoing drug-induced dyskinesias.

However, several observations are difficult to reconcile with the rate model. For instance, lesions of the thalamus do not lead to significant bradykinesia or akinesia, and lesions of the GPi do not result in dyskinesias, as one would expect if reduced pallidal output was sufficient to induce involuntary movements. These inconsistencies and the findings of recent physiological studies suggest that other features of basal ganglia discharge, particularly altered pattern changes, play a more important role than discharge rate.

Among the most prominent changes in discharge patterns in the basal ganglia of patients with PD is the development of oscillatory phenomena. Abnormal oscillations, particularly in the β -range of frequencies, have been identified in the activity of single neurons in the GPi, SNr, and STN in animals and patients and, more recently, in local field potential recordings in patients. Local field potential studies, performed with implanted deep brain stimulation (DBS) electrodes in the STN and other basal ganglia areas, have demonstrated the presence of local field potential oscillations in the 10- to 25-Hz (β) range in the STN, GPi, and cortex in unmedicated patients with PD. The β -band oscillations give way to oscillations in the 60- to 80-Hz range when the patients are treated with levodopa or the STN is stimulated at high frequencies.⁶

Another parkinsonism-related abnormality is the emergence of synchrony between neurons. Under physiological conditions, basal ganglia activity is specific in its relation to movement parameters and body part and appears to be segregated even at the cellular level, where neighboring neurons are rarely found to fire in synchrony. In parkinsonism this level of segregation is lost, and the discharge of neighboring neurons is often found to be correlated and abnormally synchronized.

Parkinsonism as a Circuit Disorder

The available anatomical and physiological studies strongly suggest that parkinsonism results from dopamine loss in the basal ganglia, which induces neuronal discharge abnormalities within the entire motor circuit. At the cortical level, this manifests itself in abnormalities in cortical activation patterns during movement tasks. Some or all of the parkinsonian signs appear to arise from abnormal basal ganglia activity, including bursts of firing or oscillatory discharge patterns, that functionally disable related thalamic and cortical areas.

Surgical Treatments for PD

The belief that PD and other movement disorders are circuit disorders is reinforced by the evidence and success of functional neurosurgical treatments for these conditions. Two general types of procedures are performed: ablations and long-term DBS.

Unilateral lesioning in the sensorimotor territory of the GPi results in significant contralateral antiparkinsonian effects and significantly reduces drug-induced involuntary movements. Unfortunately, pallidotomy cannot be performed bilaterally because of a high incidence of lesion-induced dysarthria. An alternative lesioning procedure, subthalamotomy, which can be performed bilaterally, was also shown to be effective in PD.

For DBS, an electrode is introduced into the sensorimotor portions of the STN or GPi, and high-frequency stimulation is applied via an implanted, externally programmable pulse generator. In appropriate patients, DBS, which can be performed bilaterally, can markedly reduce the intensity and duration of off-periods, increase the duration of on-periods, and effectively reduce dyskinesias.

The mechanisms of action of DBS are more complex than those of ablation, which simply interrupts abnormal activity. For instance, STN DBS may inhibit the somata of STN cells through activation of local GABA release from GPe afferents while activating STN output fibers, leading to increased glutamatergic excitation of the GPi and SNr.⁷ Spread of electrical current from the stimulation site in the STN to passing pallidothalamic fibers may also contribute to the effects of STN DBS.

Although this issue is complex and still unsettled, the available evidence suggests that the beneficial effects of STN DBS result from activation of STN efferents and the resulting favorable modulation of discharge patterns in the GPi that are propagated throughout the thalamocortical pathways. Regardless of the precise mechanism at work, functional imaging studies have demonstrated that DBS of the STN results in a relative normalization of cortical activation patterns, both at rest and with movement.⁸ The finding that ablation and DBS are effective only when they are performed specifically within the sensorimotor territories of the motor circuit strongly supports the concept that in PD, the motor circuit has been commandeered by abnormal oscillations and other pattern abnormalities and that more normal function can be achieved by elimination or modification of the abnormal basal ganglia output.

Dystonia is a hyperkinetic movement disorder that may be viewed as a circuit disorder. Dystonia is a heterogeneous condition characterized by the presence of involuntary twisting movements, especially during attempted movement, as well as abnormal postures, muscular co-contraction, and overflow phenomena in which muscle activation spreads inappropriately and excessively to other regions.

Most of our knowledge of the abnormalities in motor circuit activity in dystonia comes from investigation of patients with primary focal forms of dystonia and autosomal dominant cases of generalized torsion dystonia. Neuroimaging studies in these patients have demonstrated characteristic changes in the motor circuit both at rest and with movement. Although the lack of a suitable primate model of dystonia has limited investigation of the circuit abnormalities that underlie dystonia, the available data from neuroimaging and recordings in patients undergoing surgery indicate that dystonia and PD are grossly similar with regard to indirect-pathway overactivity and pattern abnormalities of single-cell discharge in the GPi. However, in contrast to the situation in PD, the direct pathway appears to be overactive in dystonia, resulting in a net reduction in GPi activity.⁹ Although reduced GPi output to the thalamus may then enhance thalamocortical activation, it is most likely that changes in patterning and synchrony of discharge are largely responsible for the manifestations of the disease.

In cases of focal dystonia, additional abnormalities of sensory processing, widespread reductions in cortical inhibition, and aberrant organization of somatosensory cortical maps have been demonstrated.¹⁰ These findings have given rise to the concept that abnormal motor learning or excessive neuroplasticity may play a role in dystonia.

The success of surgical treatments for PD has led to trials of pallidotomy and more recently DBS, both targeting the sensorimotor portions of the GPi, for cases of advanced drug treatment-resistant dystonia. These approaches have been highly successful, particularly in cases of generalized dystonia. It is common to see a temporal delay (up to several months) between the surgical intervention and maximal benefit, supporting the hypothesis that dystonia involves aberrant neuroplasticity.

OTHER MOVEMENT DISORDERS

Other hyperkinetic disorders, such as ballismus and chorea, also appear to result from selective involvement of portions of the motor circuit. In the case of ballismus, the disorder results from lesioning or inactivation of the sensorimotor portion of the STN. Chorea may result from lesions of the putamen, the STN, or rarely the thalamus. Both ballismus and chorea are associated with decreased levels of pallidal output. Ablation and DBS within the sensorimotor portions of the GPi are highly effective for reducing drug-induced dyskinesias, ballismus, and Huntington chorea.

The circuit disorder concept has been extended from movement disorders to include neuropsychiatric conditions, such as obsessive-compulsive disorder (OCD) and Tourette syndrome. In OCD, portions of the limbic circuit that originate in the orbitofrontal cortex appear to be involved, and interventions ablating or stimulating portions of the limbic circuitry are now being explored for severe drug-resistant cases. In Tourette syndrome, with its mix of motor and complex tics, OCD, and attention-deficit/hyperactivity disorder, limbic, associative, and motor circuits of the basal ganglia are implicated, and surgical interventions aimed at motor and limbic portions of the basal ganglia or thalamus are currently under investigation as promising new treatments.

CONCLUSIONS

Considerable evidence is now available to indicate that hypokinetic movement disorders, such as PD, and hyperkinetic disorders, such as dystonia, ballismus, and chorea, represent circuit disorders, which result from varying forms of abnormally patterned activity throughout the motor circuit of the basal ganglia. The specific clinical features of these disorders may depend on the unique combination of changes in discharge rate, pattern, and synchronization of discharge and varying degrees of involvement of individual motor subcircuits. Remarkably, these heterogeneous disorders all respond to the same surgical approaches, which either remove or modify the abnormal activity within the larger motor circuit. Such interventions may work by (nonspecifically) freeing thalamocortical and brainstem motor systems from abnormal and disruptive basal ganglia influences. Evidence indicates that the brain can compensate far better for the loss of basal ganglia output produced by ablation than for the corrupted output that characterizes the individual movement disorders and that neuromodulation (eg, DBS) is a highly effective, less invasive, and more flexible alternative to ablation.

In addition to movement disorders, neuropsychiatric conditions such as OCD and Tourette syndrome appear to arise from circuit dysfunction within the non-motor loops. Treatment of these conditions and others, such as severe intractable depression, is being revolutionized by the application of the neurosurgical techniques originally developed for the treatment of movement disorders.

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