6 THE BASAL GANGLIA

CHAPTER OVERVIEW

The basal ganglia may well come to represent the "ugly duckling" of the central nervous system. As knowledge of these structures has expanded, so too has our appreciation not only of their functional but also of their structural complexity. From a structural standpoint, new insights are constantly emerging with regard to their topographical boundaries, internal cytoarchitecture, intrinsic and extrinsic connections, and neurochemical substrates. The basal ganglia long have been viewed as being an integral part of the motor system. The identification of specific feedback loops among the cortex, basal ganglia, and thalamus involving both direct and indirect pathways, along with improved understanding of underlying neurotransmitter systems, have provided us with better insights into how these structures might contribute to both normal and abnormal movements. Equally as exciting, however, has been the relatively recent appreciation of the richness of basal ganglia connections, particularly those to prefrontal and limbic cortices. The latter, forming what might be characterized as independent neural networks subserving multiple cognitive and emotional behaviors, suggest that the basal ganglia may play an intricate role in modulating much more than simply motor expression. The concept of multiple feedback loops, especially those involving what has become recognized as the ventral striatal and ventral pallidal systems, have offered clues for a better understanding of a number of behavioral disturbances and psychiatric disorders. Knowledge of these systems along with their neurochemical substrates likely also holds the key to continued improvements in the treatment of both neurological and psychiatric disorders.

In the course of this chapter, the reader will first find a review the basic anatomy of the basal ganglia. Particular emphasis will be devoted to exploring their interrelationships with other brain structures, forming what has been characterized as multiple and at least quasi-independent neural networks, as mentioned above. Next, specific symptoms and neurobehavioral syndromes associated with lesions or functional disturbances involving various components of these networks will be explored. While in this chapter special attention will be paid to motor disturbances, the groundwork will be laid for trying to understand the role of the basal ganglia in mental and emotional disorders, a topic that will be further explored in Chapter 11. Finally, hypotheses regarding the potential role of the basal ganglia in normal behavior, both with regard to motor and non-motor activities will be reviewed. The reader is directed to Chapter 3 and Chapter 9 (Part III) for additional discussions of the probable roles of the cerebellum and various cortical regions, respectively, in motor and other behavioral expressions.

INTRODUCTION

The basal ganglia, in the general clinical connotation of the term, refers to a collection of subcortical nuclear masses that traditionally have been associated with the "extrapyramidal" motor system.[1] From a strict anatomical perspective, the term "basal ganglia" refers to those nuclear masses of the telencephalon that lie beneath the cortical mantle. These include the **caudate nucleus**, **putamen**, **globus pallidus**, **claustrum**, **amygdala,** and other basal–frontal nuclei, such as the **nucleus accumbens** and **substantia innominata**.[2] However, it is not uncommon for only the first three of these structures (the caudate nucleus, putamen, and globus pallidus) to be mentioned when clinicians discuss lesions of the basal ganglia.[3] All three structures have strong anatomical, neurochemical, and functional connections with the cerebral cortex and thalamus. However, they also have significant connections with other subcortical nuclei, particularly the subthalamus, ventral tegmental area, and the

substantia nigra. These two latter areas represent the major sources of dopamine, one of the neurotransmitters most frequently associated with this system. Lesions in any of these areas can result in motor or other behavioral disturbances. Thus, when referring to the "basal ganglia" as an *anatomical entity*, the most common connotation is probably that of the caudate nuclei, putamen, and globus pallidus. However, when speaking of the basal ganglia as a *functional system*, the subthalamus, ventral tegmental area, substantia nigra, as well as parts of the thalamus proper are typically included.

There are several other terms that often are applied to portions of the basal ganglia that require definition. Unlike the term "basal ganglia," whose referents may vary, there appears to be more consensual agreement with respect to the following appellations. The term **corpus striatum** refers to the caudate nucleus, putamen, and globus pallidus.Thus it is comparable to but more precise than the term "basal ganglia" in its most common usage. In contrast, the terms **striatum** or **neostriatum** refer collectively to just the caudate nucleus and putamen. These structures share similar histology and general patterns of connectivity and in fact are joined anatomically in their most rostral aspects prior to being separated by the fibers of the internal capsule. The nucleus accumbens, which appears to represent a ventral extension of the rostral caudate and putamen (see below), is commonly referred to as the **ventral striatum**. The putamen and globus pallidus also are grouped together and referred to as the **lentiform** or **lenticular nuclei,** because of their wedge or "lens" shaped appearance, both in coronal and axial sections. Finally, the globus pallidus is sometimes known as the **pallidum** or **paleostriatum** (Table 6–1).

Just as there may be some confusion when considering the anatomy of the basal ganglia, their functional significance is also a bit of a mystery.[4] As noted above, the basal ganglia long have been considered an integral part of the motor system. Their major influence on peripheral motor systems appears to be via the corticospinal or corticobulbar tracts (i.e., the "pyramidal" system) by way of thalamocortical feedback loops or pathways. It is predominately through these thalamocortical feedback loops that the basal ganglia are believed to help "fine tune" cortically generated movements. As will also be noted, although the consequences of lesions or disease to the basal ganglia on the motor system have been well documented, there still is considerable debate when attempting to define their contribution to normal motor activities.

In addition to the more traditional association between the basal ganglia and motor functions, we also will see that a substantial portion of the afferent and efferent connections of the basal ganglia extend well beyond the boundaries of the sensorimotor cortices. The more recent discoveries of extensive connections with prefrontal and corticolimbic structures suggest that the basal ganglia likely exert significant influences on cognitive, emotional, and

Table 6–1. Various Nomenclature for Basal Ganglia Nuclei

Term	*How Used*	*Nuclei*
Basal ganglia	Broad anatomical (exceedingly rare)	Caudate, putamen, globus pallidus, claustrum, amygdala, frontobasalar n.
Basal ganglia	Common anatomical	Caudate, putamen, globus pallidus
Basal ganglia	Clinical/functional	Caudate, putamen, globus pallidus, substantia nigra, subthalamus.
Corpus striatum		Caudate, putamen, globus pallidus
Striatum (neostriatum)		Caudate and putamen
Lentiform (lenticular) nucleus		Putamen and globus pallidus
Paleostriatum (pallidum)		Globus pallidus

motivational systems. However, as with their motor functions, determining the nature and scope of these influences is often difficult. Before addressing these functional issues, it might be helpful to review the anatomy of these various nuclei and their interconnections.

ANATOMY

Caudate Nuclei

The caudate nuclei are two, deep, midline subcortical nuclear masses that developed into elongated "C"-shaped structures as the brain developed and the telencephalon expanded into its current state. The shape of the caudate nuclei resembles an elongated tadpole with an enlarged portion or "head" located anteriorly or rostrally, a tapering body and a long, slender "tail" that curves in a posterolateral and ventral direction. As can be seen in Figures 6–1 and 6–2(d–h), the head forms a distinct bulge on the lateral wall of the frontal horn of the lateral ventricle, with the body maintaining a comparable position along the lateral wall of the body of the lateral ventricle. The tail ends up lying in the dorsum or roof of the inferior (temporal) horn of the lateral ventricle, terminating near the amygdala in the anteromedial temporal lobe. When viewed in either a horizontal or coronal section, the head of the caudate nucleus protrudes into the lateral wall of the anterior horns of the lateral ventricles, creating their characteristic "boomerang" shape. The caudate is continuous with the putamen in its most rostral aspect, but the caudate and putamen soon become separated into distinct nuclei by the anterior limb of the internal capsule (Fig 6–1a). At this level, the nucleus accumbens represents the ventral extension of the conjoining of these nuclear masses. Throughout its course, the stria terminalis, a fiber pathway connecting the amygdala with the hypothalamus and septal regions of the basal forebrain, lies adjacent to the caudate.

Putamen

As previously noted, the putamen, which is histologically similar to the caudate, is continuous with the latter in their more rostral extensions (see Fig 6–2c, right side). Even as the internal capsule cleaves these bodies, strands of gray matter linking the two still may be appreciated traversing the internal capsule in Figure 6–1a. These strands are known as the *transcapsular striae* or *cell bridges*. As can be seen in the accompanying figures, as it progresses caudally, the putamen becomes clearly separated from the head of the caudate by the anterior limb of the internal capsule. The external capsule and the claustrum border the lateral aspect of the putamen. The globus pallidus lies on its medial surface, the two being separated by the **lateral** (*external*) **medullary lamina** of the globus pallidus, which may be seen in Figure 6–1c. Recall that the putamen and globus pallidus, which form a triangular or wedge-shaped mass, are collectively referred to as the "lenticular" nuclei. This perhaps can be seen most clearly on the axial sections (Figure 6–2) where the lenticular nuclei are lateral to and bounded by the anterior and posterior limbs of the internal capsule. While both the caudate and putamen receive considerable input from the cortex (see below), the putamen receives a disproportionate share from the primary sensorimotor cortices, while the caudate is more closely related to cortical association areas.

Globus Pallidus

The globus pallidus (literally, *pale sphere*) phylogenetically is an older structure (paleostriatum). As its name implies it has a somewhat "paler" appearance than other basal ganglia structures as a result of the multitude of myelinated fibers traversing it. The globus pallidus constitutes the medial portion of lenticular nuclear complex. It is separated from the putamen

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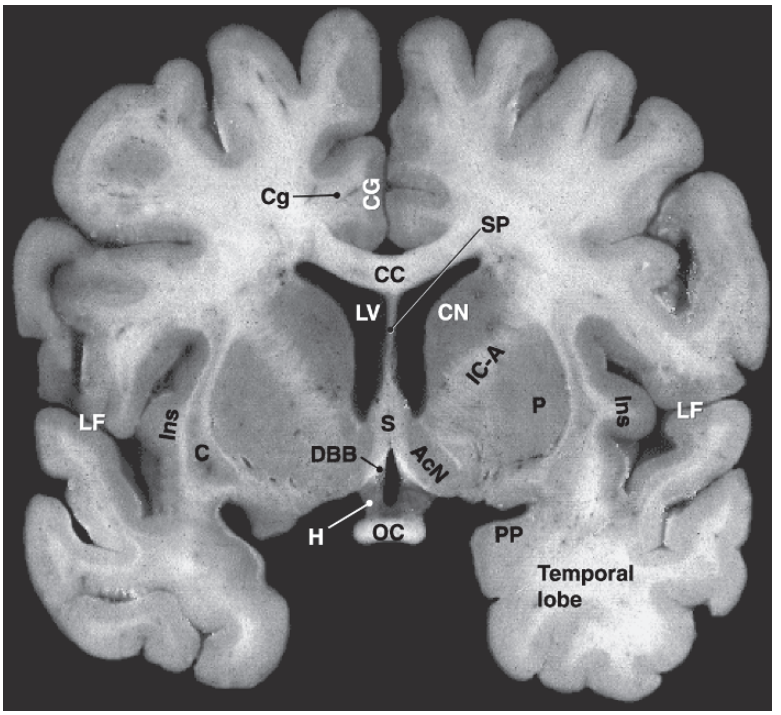

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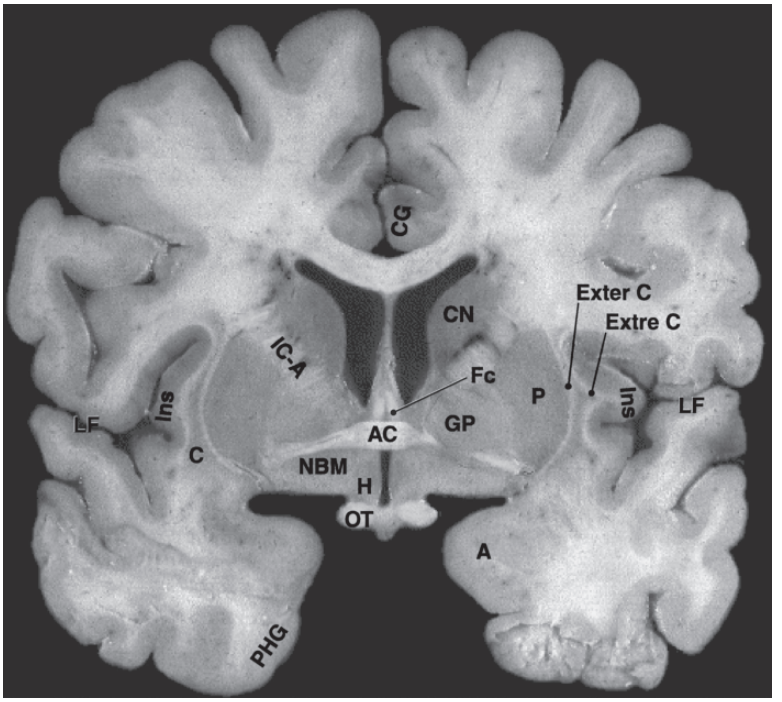

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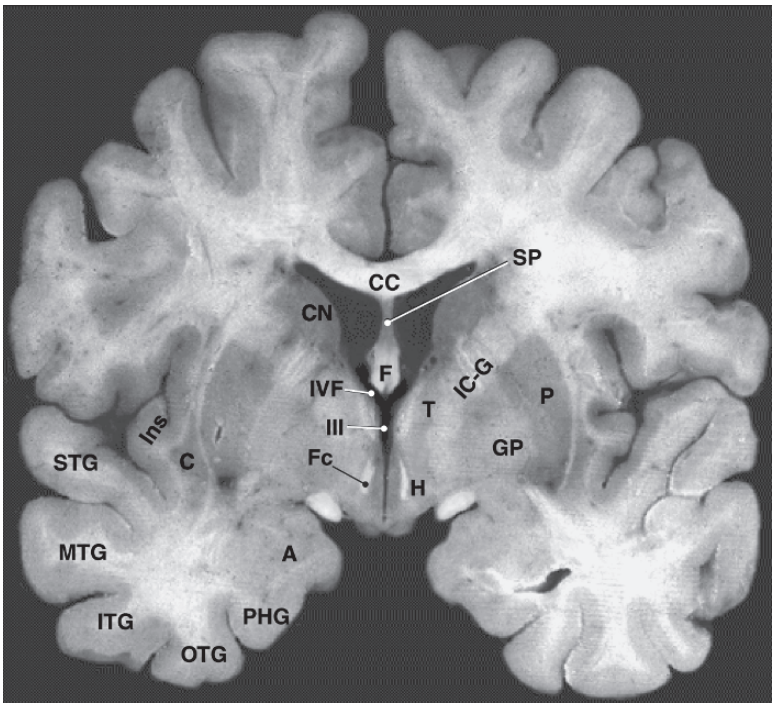
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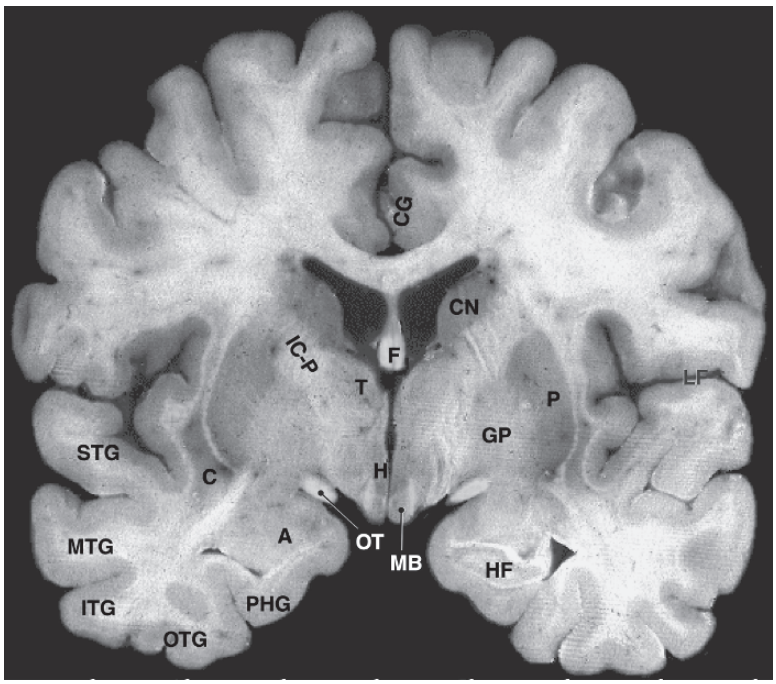
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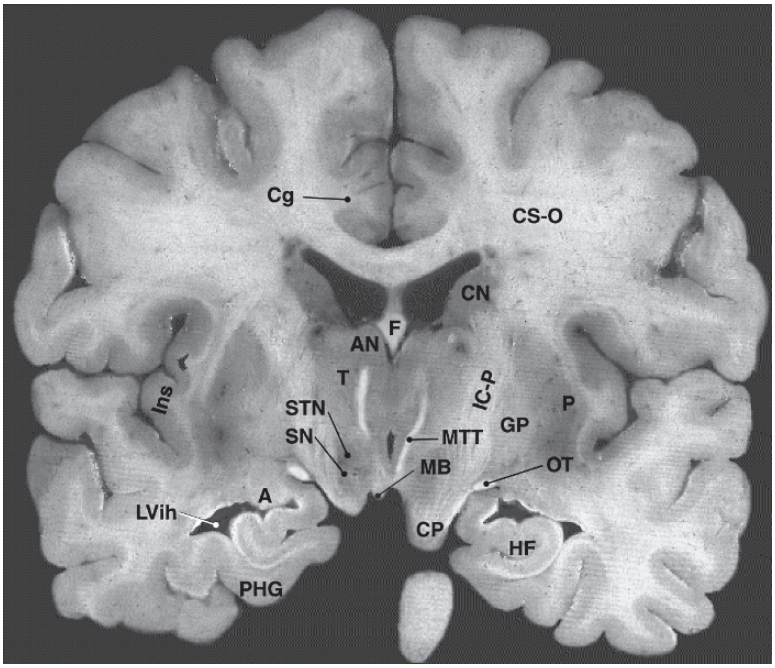

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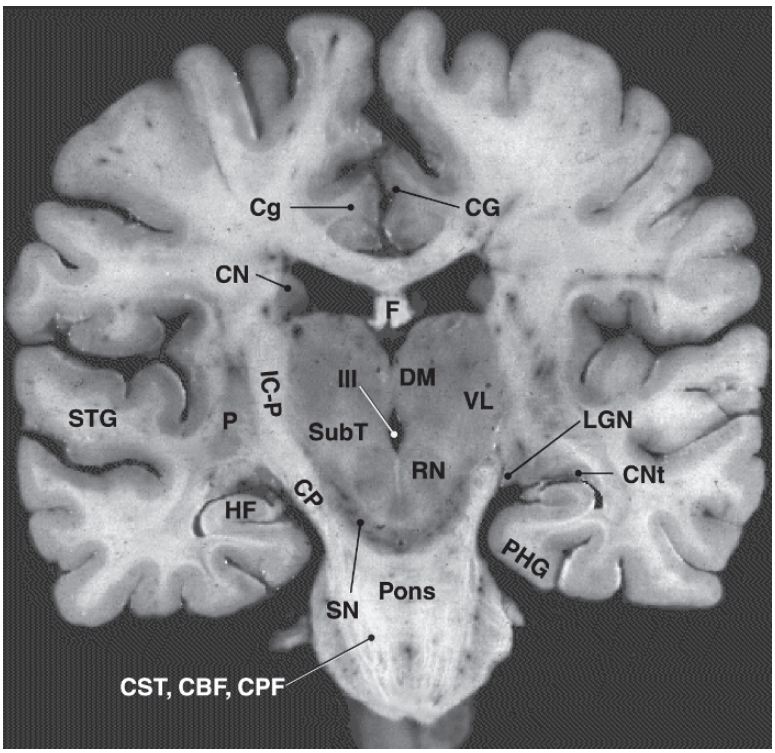

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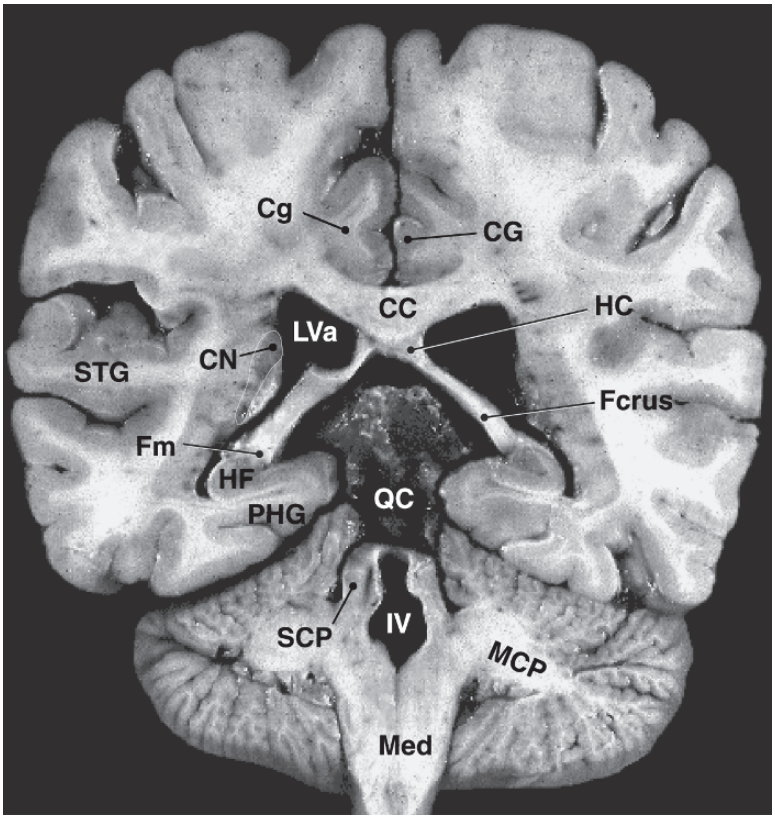

Figure 6–1. Coronal sections through the basal ganglia. Brain images were adapted from the *Interactive Brain Atlas* (1994), courtesy of the University of Washington.

III, 3rd ventricle
IV, 4th ventricle
A, amygdala
AC, anterior commissure
AcN, nucleus accumbens
AN, thalamus (anterior nucleus)
BN, basal nuclei
C, claustrum
CA, cerebral aqueduct
CC, corpus callosum
CCg, corpus callosum (genu)
CCs, corpus callosum (splenium)
CG, cingulate gyrus
Cg, cingulum
CN, caudate nucleus (head)
CNb, caudate nucleus (body)
CNt, caudate nucleus (tail)
CP, cerebral peduncle
CS-O, centrum semiovale
CBF, corticobulbar fibers
CPF, corticopontine fibers
CST, corticospinal tract
DBB, diagonal band of Broca
DM, thalamus (dorsal medial nucleus)
DN, dentate nucleus
Exter C, external capsule
Extre C, extreme capsule
F, fornix
$F_{C,}$ fornix (columns of)
$F_{crus,}$ crus of fornix
$F_{M,}$ fimbria
GP, globus pallidus
GR, gyrus rectus
H, hypothalamus
HC, hippocampal commissure
HF, hippocampal formation
IC, inferior colliculus
IC-A, internal capsule (anterior limb)
IC-G, internal capsule (genu)
IC-P, internal capsule (posterior limb)
Ins, insular cortex
ITG, inferior temporal gyrus
IVF, foramen of Monro
LF, lateral fissure

by the lateral medullary lamina and from the thalamus by the internal capsule. The globus pallidus is divided into two components: a **medial** or **internal segment** (*GPi*) and a **lateral** or **external segment** (*GPe*) by a **medial** (*internal*) **medullary lamina**. Although both segments receive afferent input from the caudate and putamen, as will be seen later, the pattern and functional significance of their other connections would appear to differ significantly. For now, one might simply note that while the output of the external segment is directed primarily to the substantia nigra and subthalamic nuclei, the medial or internal segment's main output is to the thalamus. The latter represents the primary source of the lenticulothalamic fibers, which in turn constitute a major part of the cortical feedback loops via the thalamus (see below).

Ventral Striatum and Ventral Pallidum

On coronal brain sections at the level of the anterior commissure and optic chiasm (see Figure 6–1b), an area of gray matter can be found lying between the horizontal plane of the anterior commissure and the ventral surface of the brain. With the exception of the preoptic nuclei of the hypothalamus that occupy part of this region, this area was once simply referred to as the **substantia innominata**, reflecting the anatomists' uncertainty as to the specific origin or nature of these nuclei. Now it is recognized that this area includes the **basal nucleus of Meynert** (the origin of multiple cholinergic pathways), the extended amygdala,[5] as well as the ventral, posterior extension of the nucleus accumbens or the ventral striatum and the ventral extension of the globus pallidus or ventral pallidum. As we shall see, these ventral portions of the corpus striatum intimately are associated with structures that are related to emotional processing and motivation (Heimer, 2003). Furthermore, these ventral portions of the basal ganglia also contribute to cortical feedback loops through the thalamus (see discussion of cortical circuits later in this chapter).

Subthalamus

The subthalamus, which lies below or caudal to the thalamus around the lateral walls of the third ventricle (Figure 6–1e,f), contains several discrete nuclear groups. These nuclear groups include the **zona incerta**, **field H of Forel**, and the **subthalamic nucleus of Luys**.

Figure 6–1.

LGN, lateral geniculate nucleus
LV, lateral ventricle
$LV_{A,}$ Lateral ventricle (atrium)
$LV_{IH,}$ lateral ventricle (inferior horn)
MB, mammillary body
MCP, middle cerebellar peduncle
Med, medulla
MGN, medial geniculate nucleus
MI, massa intermedia
MTG, middle temporal gyrus
MTT, mammillothalamic tract
OC, optic chiasm
OT, optic tract
OTG, occipitotemporal gyrus
P, putamen
PC, posterior commissure
PHG, parahippocampal gyrus
PP, prepyriform cortex
Pul, pulvinar
QC, quadrigeminal cistern
RN, red nucleus
S, septal nuclei
SC, superior colliculus
SCP, superior cerebellar peduncle
SN, substantia nigra
SP, septum pellucidum
STG, superior temporal gyrus
STN, subthalamic nucleus
SubT, subthalamus
T, thalamus
V, vermis (of cerebellum)
VA, thalamus (ventral anterior nucleus)
VL, thalamus (ventral lateral nucleus)

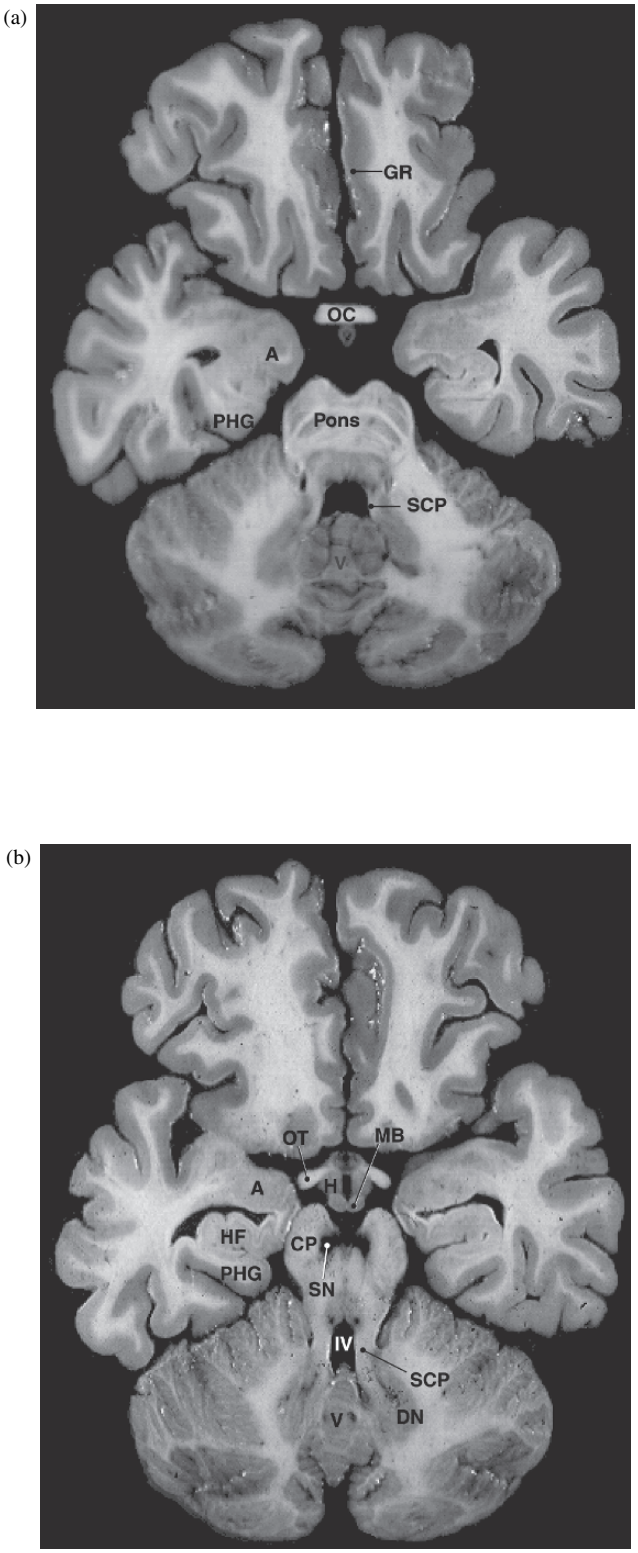

Figure 6–2. Axial sections showing structures of the basal ganglia. Brain images were adapted from the *Interactive Brain Atlas* (1994), Courtesy of the University of Washington.

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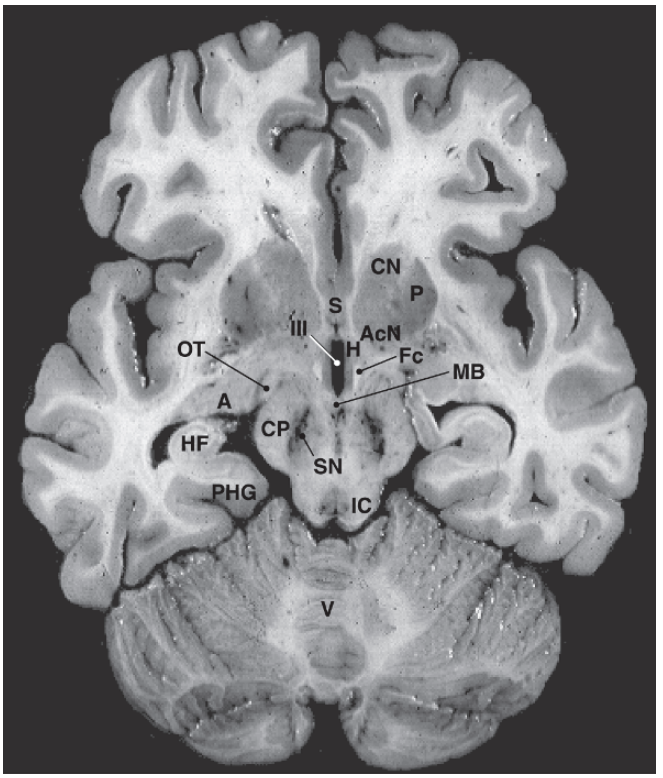

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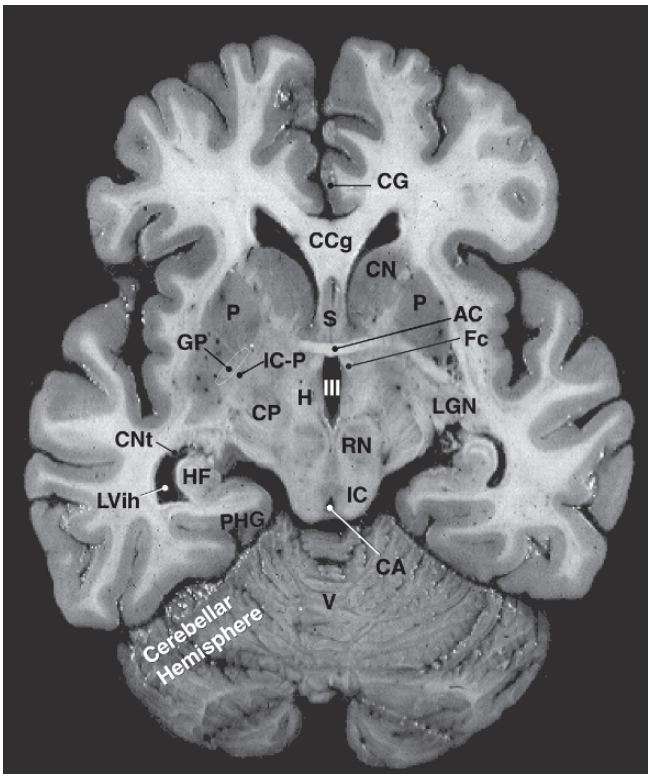

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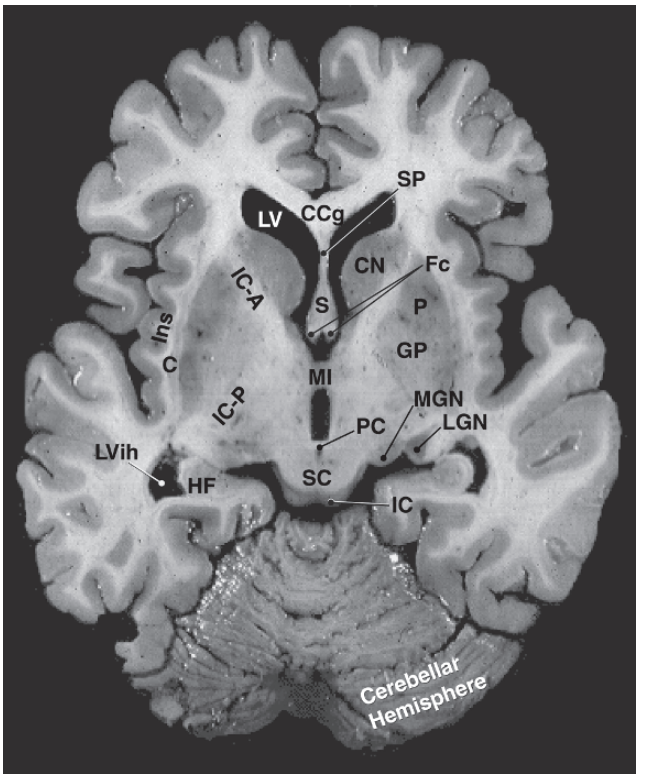

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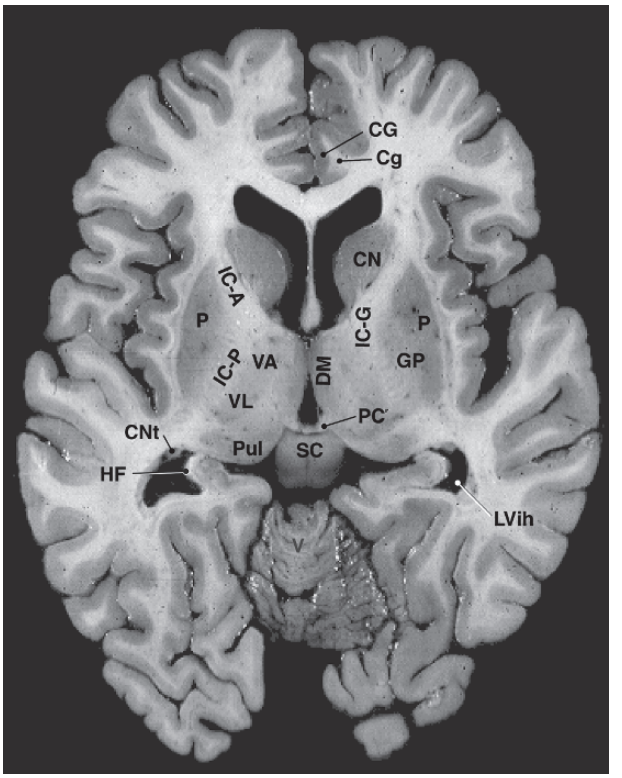

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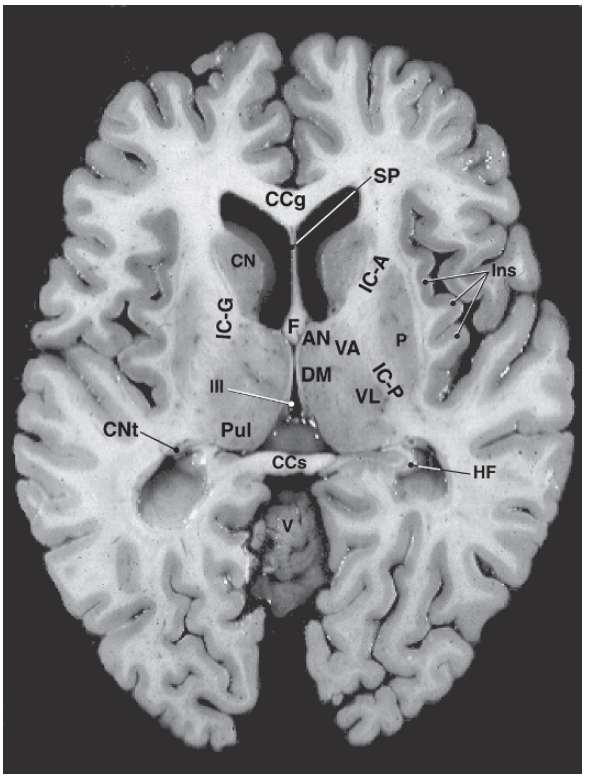
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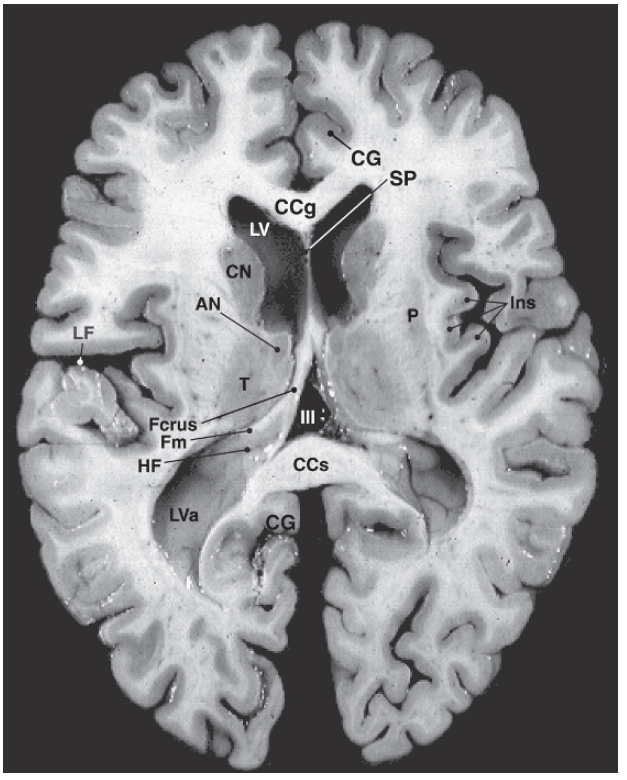
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This latter nuclear group is more or less continuous with the substantia nigra in its caudal extension and plays an integral part in the corticothalamic feedback loops to be discussed later.

Substantia Nigra

As noted in Chapter 4, the substantia nigra lies in the tegmentum of the rostral midbrain just dorsal to the cerebral peduncles (Figure 6–1e,f and 6–2b,c). It is composed of two major cellular groupings: the more medially located **pars compacta** and the **pars reticularis**, which lies more laterally. The pars compacta, along with the adjacent **ventral tegmental area**, are the source of the dopaminergic pathways. The pars reticularis is structurally similar to the medial segment of the globus pallidus, and like the latter is a major source of efferent fibers to the thalamus.

CONNECTIONS

Probably the most common perception of the functions of the basal ganglia relates to their role in **feedback loops** that facilitate the smooth execution of movements or facilitate transitions between individual motor acts. These feedback loops include the cortex, corpus striatum, substantia nigra, and subthalamic and thalamic nuclei. However, as we later trace several of these major pathways or connections, it will become clear that the role of the basal ganglia is far more complex than initially thought and as noted above likely contributes to various cognitive and emotional aspects of behavior. These pathways and the effects of their disruption will be discussed below. First, it might be helpful to review the major inputs and outputs of the corpus striatum and related structures.

Striatum (Caudate and Putamen)

Afferents

The primary input to the striatum is from the cerebral cortex via both the internal and external capsules. This input is highly topographically organized and is not restricted to regions that are directly associated with motor control, but comes from diverse cortical areas, particularly association cortices. Both the caudate and putamen receive inputs from sensorimotor areas of the cortex and from frontal, parietal, and temporal association areas. These inputs, however, are differentially distributed such that the putamen receives the majority of its input from sensorimotor cortex, while the caudate has more extensive input from non-motor, association areas. The caudate receives projections throughout its length, but a disproportional amount of fibers enter its anterior enlargement or "head." The majority of these latter fibers emanate from the tertiary or "prefrontal," dorsolateral association cortices, suggesting the caudate plays a role in the more cognitive aspects of motor or other "executive" types of behavior. Hence, lesions of the caudate can result in "frontal-type" cognitive deficits (Cummings & Benson, 1990).

In contrast, the orbital and mesial frontal cortices appear to project primarily to the ventromedial portions of the striatum, providing an anatomical basis for still further functional differentiation within the striatum. Specifically, the nucleus accumbens receives its inputs largely from structures associated with the limbic system. These sources include the anterior cingulate gyrus, the basolateral amygdala, and parts of the parahippocampal gyrus. The extended amygdala (including the bed nucleus of the stria terminalis) is structurally adjacent to the ventral striatum and may influence it either directly or through the amygdala proper via the stria terminalis. These connections may allow motivational influences to impact on the basal ganglia (e.g., the emotional valence of stimuli; see Chapter 8).

In addition to these more rostral inputs, the striatum also receives considerable input from the pars compacta of the substantia nigra and from the adjacent ventral tegmental area. Both of these areas represent dopamine projections. **Serotonergic** pathways from the raphe nuclei in the brainstem also provide input to the striatum. Finally, as we shall see, in addition to feedback loops from the cortex and substantia nigra there also is a thalamic loop. In this case, the afferent connections primarily emanate from the intralaminar (e.g., centromedian) and midline thalamic nuclei.

The cortical input to the striatum is largely if not exclusively **glutaminergic** and is facilitatory or excitatory in nature. The **dopamine pathways** from the substantia nigra (pars compacta) and ventral tegmental area appear to have either facilitatory or inhibitory influences depending on their site of action. As will be seen in the following paragraph, the striatum sends projections to both the internal and external sections of the globus pallidus. The internal globus pallidus, in turn, projects directly to the thalamus, whereas the cells of the external segment, although also eventually projecting to the internal segment and onto the thalamus, do so largely by way of the subthalamus. The dopaminergic pathways that project back to the striatal cells that in turn are destined for the external segment of the globus pallidus utilize D_2 type receptors and are inhibitory in nature. Those projecting to striatal cells destined for the internal segment of the globus pallidus appear to be excitatory, utilizing D_1 type receptors (Albin, Young, & Penny, 1989; DeLong, 1990; Mink & Thach, 1993). The possible clinical significance of these anatomical differences will be discussed later in this chapter when these connections are reviewed in light of certain disease processes affecting the basal ganglia. The serotonergic pathways from the raphe nuclei also tend to be inhibitory in nature.

Efferents

The primary outputs of the striatum are to the ipsilateral globus pallidus and to the substantia nigra. Projecting both to the internal and external segments of the pallidum, the output of the striatum, like its input, remains topographically organized. These various striatopallidal and striatonigral pathways are known to use **gamma-aminobutyric acid** (GABA) in their chemical transmission and are thought to be inhibitory in nature.[6] Just as depletions in dopamine have been associated with Parkinson's disease, reductions in GABA have been linked to Huntington's disease, which is associated with degeneration of the striatum, particularly the caudate nucleus. However, disturbances in neurochemical transmission involving some of these same substances that largely have been associated with the basal ganglia (e.g., dopamine, GABA, and serotonin) also appear to play a major role in many psychiatric disturbances (see Chapter 11). Again, this reinforces the notion that the various nuclei that make up the basal ganglia are more than just "motor" structures.

Globus Pallidus

Preliminary Considerations

Before reviewing the connections of the internal and external segments of the globus pallidus, a few preliminary observations may be useful. One, if not the major, role of the basal ganglia is thought to be to modulate the activity of the cerebral cortex. In accomplishing this, cortical information is funneled through the striatum to the thalamus via the internal and external segments of the globus pallidus. The thalamus in turn projects back to the cortex. While the pallidothalamic connections appear to be primarily inhibitory in nature, the thalamocortical projections are thought to be mostly facilitatory.

To keep it relatively simple, think for a moment about motor activity. In carrying out motor actions, it is necessary that certain motor groups (e.g., the target and agonist muscles) be facilitated, while other groups (antagonist muscles) be relaxed or inhibited. However, since most if not all thalamocortical output is excitatory, one way to modulate cortical activity would be to facilitate those thalamocortical connections to the agonist muscles, while inhibiting similar connections to the antagonist muscles. The "direct" and "indirect" pathways through the globus pallidus to the thalamus seem ideally suited to this task.

"Direct" and "Indirect" Pathways

As can be seen in Figure 6–3, in the **direct** pathway there are direct connections between the striatum (caudate nucleus and putamen) and the internal segment of the globus pallidus (GPi) before the latter sends its output to the thalamus. By contrast, in the **indirect** pathway the striatal nuclei first project to the external pallidal segment (GPe) and then detour through the subthalamus, before going on to the GPi and eventually to the thalamus. By tracing these connections it can be seen that by inhibiting the "inhibitory" pallidothalamic neurons (i.e., "disinhibition"), as is the situation in the "direct" pathways, the net effect

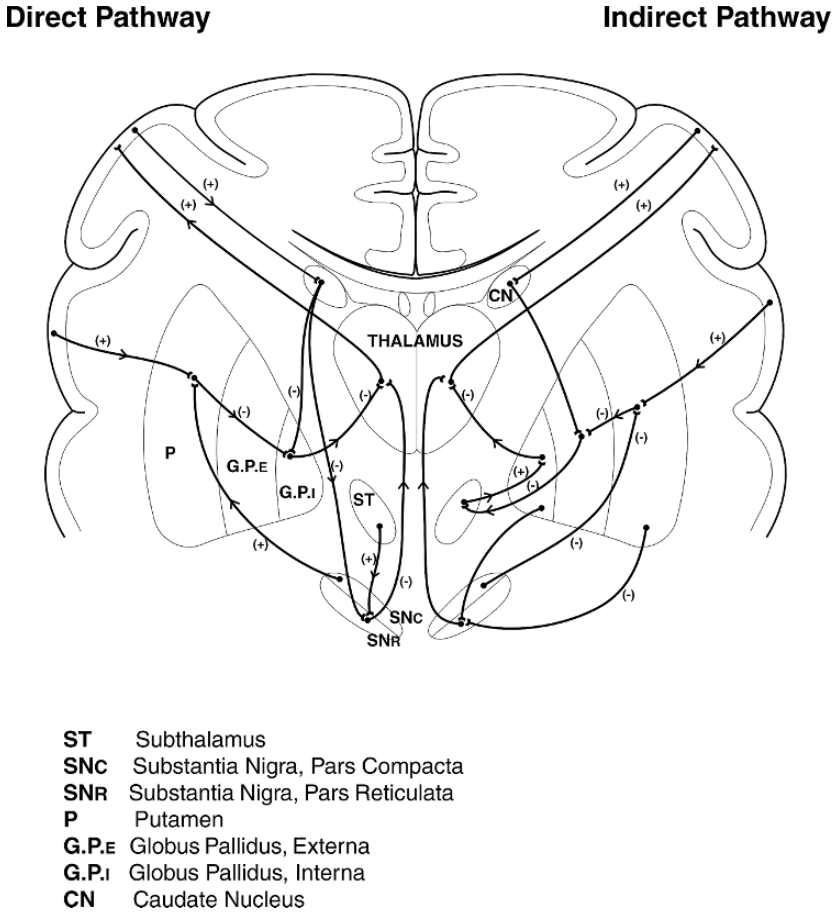

Figure 6–3. Direct and indirect cortical-basal ganglia-thalamic feedback loops. Abbreviations: (+) facilitatory pathway; (−) inhibitory pathway.

will be to disinhibit the facilitatory glutaminergic thalamocortical neurons, thus creating an **excitatory** influence on those parts of the cortex. These connections then might serve to enhance the activity of agonist muscles. On the other hand, if selected (inhibitory) pallidothalamic neurons could be facilitated (as is the case in the "indirect," striatosubthalamopallidal pathways), the net effect on the targeted thalamic neurons will be **inhibitory**. Through this latter arrangement, antagonist muscle groups effectively could be toned down (i.e., normally excitatory thalamocortical feedback will be reduced).[7] Although greatly simplified, understanding these basic connections and their positive or negative influence on postsynaptic junctions helps set the stage for the discussions to follow later.

Afferents

The main source of afferent fibers into the globus pallidus is from the caudate and putamen. These fibers project to both the internal (medial) and external (lateral) segments of the pallidum from which the direct and indirect thalamic pathways are respectively derived. The other major identified source of pallidal input is from the subthalamic nucleus. Similar to the corticostriatal projections, a strong topographical organization persists, with different corticaareas ultimately projecting to distinct portions of the globus pallidus. This topographical organization is a pattern that, for the most part, appears to be maintained throughout these corpus striatal feedback loops. The input to the globus pallidus from the striatum is GABAergic and inhibitory, while the subthalamic-pallidal connections are glutaminergic and facilitatory (excitatory).

Efferents

As previously mentioned, the striatum sends its efferent projections to both the external and internal segments of the pallidum. In the more *direct route*, the internal segment sends the majority of its efferent fibers directly to the thalamus. Whereas in the *indirect pallidothalamic pathway*, the external segment establishes connections with the subthalamic nucleus before it, in turn, sends projections back to the internal segment of the globus pallidus and then on to the thalamus. Some of the more well-established pallidothalamic connections include those to the ventral–anterior (VA), ventral–lateral (VL), and dorsomedial (DM) nuclei of the thalamus. The fibers that travel to the VA and VL nuclei tend to originate in the putamen and project back to the sensorimotor cortices. Conversely, the fibers that travel to the DM nuclei generally represent caudate projections and send fibers back to the prefrontal regions (see Chapter 7). The ventral striatum, which receives input from various limbic structures, also projects to the magnocellular portion of the dorsomedial nuclei, which in turn projects to the anterior cingulate region. Finally, other probable thalamic projections include those to intralaminar nuclei (especially the centromedian and parafascicular nuclei) which project back to the striatum.

The pallidothalamic fibers, all of which emanate from the internal segment of the globus pallidus, can take one of two routes to the thalamus. The more dorsal portion of the pallidum sends fibers medially and slightly caudally, traversing the internal capsule on their way to the thalamus. This pathway is known as the **lenticular fasciculus** (*field H2 of Forel*) (Figure 6–4). By contrast, those pallidothalamic fibers leaving the more ventral portion of the internal segment take a more caudal loop into the prerubral area before joining up with the fibers of the lenticular fasciculus and with fibers ascending from the cerebellum to form the **thalamic fasciculus** (*field H1 of Forel*). Those fibers that comprise the descending loop prior to forming the thalamic fasciculus are known as the **ansa lenticularis**. Both the fibers of the lenticular fasciculus and the ansa lenticularis are primarily **GABAergic,** and hence, are inhibitory. The globus pallidus also sends a much smaller group

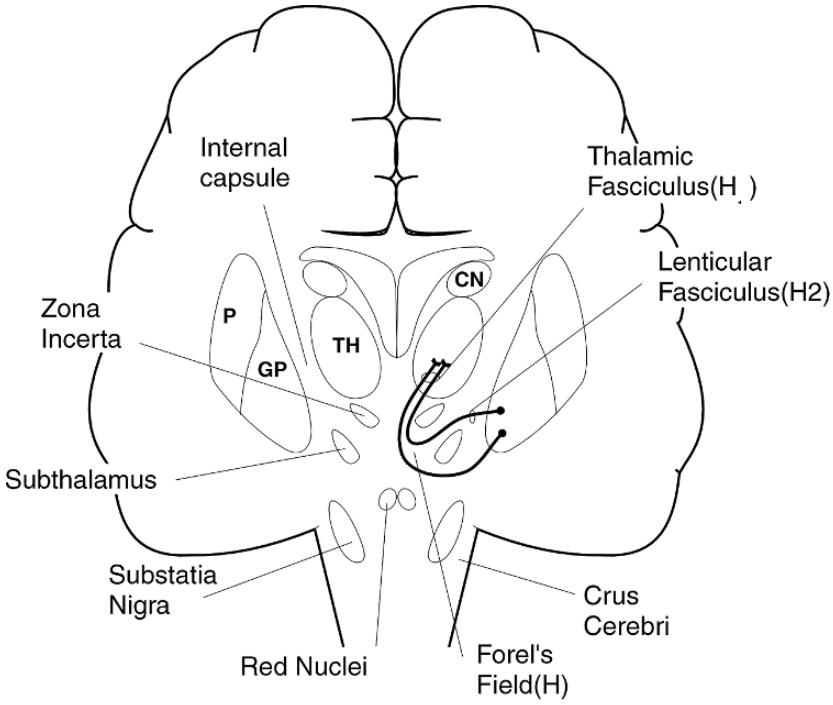

Figure 6–4. Thalamic and lenticular fasciculi.

of fibers to the habenular nuclei (epithalamus) via the **stria medullaris** and to the midbrain (pedunculopontine nuclei).

Subthalamus

Afferents

Several sources of input to this nucleus have been identified. The primary source of input, in terms of number of fibers, appears to be fibers coming from the lateral or external segment of the globus pallidus (via the **subthalamic fasciculus**). The subthalamus also receives input from the cortex, particularly the sensorimotor regions. Input also is received from the centromedian and parafascicular nuclei of the thalamus, the substantia nigra (pars compacta), and the pedunculopontine nucleus in the brainstem.[8] Like most of the other outputs of the globus pallidus, the pallidosubthalamic fibers are GABAergic and inhibitory. As in the case of the corticostriatal connections, the cortical inputs to the subthalamus are likely primarily glutaminergic (excitatory).

Efferents

The two primary outputs of the subthalamus are to the globus pallidus and to the substantia nigra (pars reticulata). Projections to the globus pallidus are to both the internal and external segments (Ma, 1997). The internal or medial segment completes the "indirect" feedback loop to the cortex (cortex → striatum → globus pallidus, external division (GPe) → subthalamus → globus pallidus, internal division (GPi) → thalamus → cortex). A smaller number of fibers from the subthalamus appear to project back to the striatum. The efferent fibers of the subthalamus are all primarily glutaminergic, and hence, have an excitatory effect on the nerve cells to which they project.

Substantia Nigra

Afferents

The most prominent inputs to the substantia nigra are those from the caudate and putamen. These inputs are largely GABAergic. Additional inputs come from the subthalamus, globus pallidus (primarily from the internal segment), and **serotonergic** fibers from the raphe nuclei. The cortex also may send a small number of fibers directly to this nuclear group. Most of the afferent connections are to the **pars reticulata** portion of the substantia nigra.

Efferents

The substantia nigra sends fibers back to the striatum, primarily from the **pars compacta**. *These nigrostriatal pathways represent the major source of dopaminergic input to the striatum*. It has been noted that these nigrostriatal connections may be either excitatory (D_1 receptors) or inhibitory (D_2 receptors), depending on the subtype of striatal dopamine receptors on which they synapse. Neurons in the caudate or putamen that project to the internal segment of the globus pallidus appear to utilize primarily **D_1-type receptors.** These synapses are **facilitatory**. On the other hand, those nigral fibers that project back to striatal cells destined for the external segment utilize **D_2 receptors** and tend to be **inhibitory**.

The **pars reticulata** portion of the substantia nigra represents the other major source of basal ganglia output to the thalamus (along with the internal segment of the globus pallidus). This (nondopaminergic) portion of the substantia nigra sends efferent fibers to the ventral anterior and ventral lateral nuclei of the thalamus. The pars reticulata also projects to the dorsomedial nucleus, which in turn projects back to prefrontal cortical areas. These nigrothalamic fibers terminate in different areas of the thalamic nuclei than do the pallidothalamic pathways, suggesting they may be mediating different functions. Additional efferent, nondopaminergic connections are sent to the superior colliculi and to the pedunculopontine nucleus (PPN). Recall that this latter nucleus (PPN) represents a confluence of cortical motor and cerebellar and basal ganglia input. Finally, the pars compacta has descending influences on the raphe nuclei (serotonergic) of the midbrain. Tables 6–2A and 6–2B provide a summary of suspected neurochemical pathways in the direct and indirect systems.

FEEDBACK LOOPS

As noted, the striatum, particularly the caudate nucleus and the ventral striatum, and nucleus accumbens receive substantial input from diverse cortical regions. Input to the putamen is primarily from the sensorimotor cortices, including the supplementary motor

Table 6–2A. Direct Neurochemical Pathways

Pathway	*Transmitter (main type)*	*Effect*
Corticostriatal	Glutaminergic	Excitatory
Striatonigral	GABAergic	Inhibitory
Nigrostriatal	Dopaminergic(D_1)	Excitatory
Striatopallidal (internal segment)	GABAergic	Inhibitory
Pallidothalamic	GABAergic	Inhibitory
Thalamocortical	Glutaminergic (?)	Excitatory
(Net effect on cortical neurons: positive)		

Table 6–2B. Indirect Neurochemical Pathway

Pathway	*Transmitter (main type)*	*Effect*
Corticostriatal	Glutaminergic	Excitatory
Striatopallidal (external segment)	GABAergic	Inhibitory
Striatonigral	GABAergic	Inhibitory)
Nigrostriatal	Dopaminergic(D_2)	Inhibitory)
Pallidosubthalamic	GABAergic	Inhibitory
Subthalamopallidal (internal segment)	Glutaminergic	Excitatory
Pallidothalamic	GABAergic	Inhibitory
Thalamocortical	Glutaminergic (?)	Excitatory
(Net effect on cortical neurons: negative)		

area on the medial surface of the hemisphere. These latter corticostriatal pathways eventually project back to these same sensorimotor areas via the VA and VL nuclei of the thalamus. The remaining corticostriatal fibers largely come from association cortices in the frontal, parietal, and temporal lobes. The majority of these connections appear to return to the frontal association cortices. Given that these pathways originate from the cortex, project to the striatum, and then back to the cortex (via the thalamus), these pathways are referred to as *corticostriatocortical loops*. Five such corticostriatocortical pathways or loops have been identified (Alexander, DeLong, & Strick, 1986) and are described below.

Motor Circuit

This loop likely originates from cortical neurons in the **primary motor, supplementary motor, primary somatosensory**, and possibly in adjacent association **cortices** (Figure 6–5). Axonal fibers project primarily to the putamen. As is probably true of all corticostriatal pathways, there are both "direct" and "indirect" routes to the thalamus via the internal and external segments of the globus pallidus, substantia nigra, and subthalamus. In the case of the "motor" circuit, the primary thalamic projection areas are the **ventral anterior** (VA) and **ventral lateral** (VL) **nuclei**, with the topographical organization being well maintained. These nuclei, in turn, project back to the primary motor, premotor, and supplementary motor cortices. While this system primarily projects back up to the cortex, some fibers exert an independent descending influence on the spinal motor pathways via the pedunculopontine nuclei in the midbrain.

Oculomotor Circuit

It might be tempting to view this loop simply as a special subset of the motor circuit that begins and ends in the **primary** and **supplementary eye fields** were it not for a few important differences. First, some of its cells of origin appear to derive from the dorsolateral prefrontal cortex. Second, while the putamen is the primary projection site in the neostriatum for the motor circuit, the oculomotor pathway appears to converge primarily in the caudate nucleus. From there fibers (again via direct and indirect routes) are sent not only to ventral anterior, but also to the **dorsomedial** (DM) **nuclei** of the thalamus. Finally, whereas the motor circuit has connections with the pedunculopontine nucleus of the midbrain, the oculomotor loop establishes connections with the superior colliculi, which, as we have noted in Chapters 4 and 5, are important in oculomotor reflexes and eye movements. This system is apparently important in executing voluntary eye movements or in conducting visual searches of one's environment.

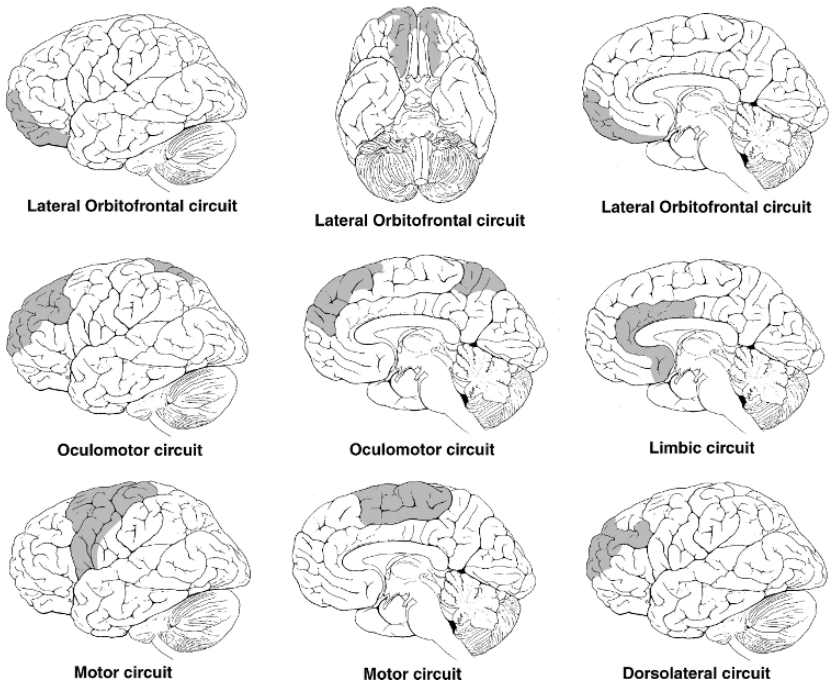

Figure 6–5. Proposed major cortical–basal ganglia circuits following Alexander, DeLong, and Strick (1986).

Dorsolateral Circuit

Again, this is where we begin to diverge from the older concepts of the basal ganglia as strictly a motor system. This "circuit" arises primarily from the **dorsolateral frontal association cortices**, although some of the parietal and temporal association areas also appear to contribute to the afferent side of this basal ganglia loop. Most of the frontal association fibers travel to the head of the caudate, while the parietal and temporal cortices likely project to the body and tail of this nucleus. After going through the usual pallidonigral loops, this system projects both to the **VA and DM nuclei** of the thalamus. From there, the majority of the thalamocortical fibers end up back in the dorsolateral or "prefrontal" association cortices. Because of its connections, this loop is thought to play a role in the higher cognitive or "executive" functions normally associated with this part of the brain (see Chapter 9).

Lateral Orbitofrontal Circuit

This circuit appears to represent a transition between the dorsolateral loop described above and the "limbic" loop to be described below. As the name implies, the origins of the corticostriatal fibers appear to be generally in the **frontal orbital regions**, although this system also may pick up some fibers from the anterior temporal cortices as well. Whereas the dorsolateral circuit tended to project most heavily to the dorsal head of the caudate, this system tends to utilize the more ventral or ventromedial portions of the head of the caudate. Similar to the dorsolateral circuit, the primary thalamic areas on which these fibers converge are also the **VA** and **DM** nuclei. However, their relative distributions within these nuclei are different. The lateral orbitofrontal system tends to concentrate on

the magnocellular portions of these nuclei, in contrast to the parvicellular layer of the VA and probable more diffuse projection to the DM nuclei for the dorsolateral circuits. As is typical of these circuits, the resulting thalamocortical projections are back to the lateral orbitofrontal cortices. As we shall see later in discussing the limbic system and the frontal cortex, these orbitofrontal areas probably are important in mediating basic emotional drives such as those involved in self-defense (e.g., fight or flight) or appetitive instincts (e.g., sex attraction or hunger) and environmental contingencies or learned "social controls." Hence, disturbances of this circuit may manifest as behavioral changes (e.g., disinhibition, emotional lability). Conversely, disorders of this system that lead to excess (as opposed to deficient) activation might lead to over-control as opposed to diminished control. One example of the latter is thought to be obsessive–compulsive disorders (OCD), which have been linked with increased metabolism in this circuit (see: LaPlane et al., 1989; Insel, 1992; Mega & Cummings, 1994; Modell et al., 1989; Stahl, 1988; Baxter et al., 1992; Zald & Kim, 1996a,b).

Limbic Circuit

In the limbic circuit, striatal input primarily is from allocortex (or juxta-allocortex), including the anterior **cingulate gyrus,** medial **orbitofrontal** areas**, hippocampal gyrus,** and perhaps some portions of **temporal** neocortex. The striatal and pallidal projections also are distinct. In this case, the incoming fibers project to the region of the nucleus accumbens or ventral striatum and from there to the precommissural pallidum. These areas then project to the DM nucleus of the thalamus, which in turn projects back to the anterior cingulate and medial orbitofrontal cortex.[9] As we shall see in later chapters, disruption of these areas often leads to apathy or reduced drive or motivation and in extreme cases akinetic mutism. As was seen with the lateral orbitofrontal circuits, disturbances of this system often have been linked with psychiatric symptomatology, particularly OCD and certain features of schizophrenia. While it has been suggested for some time that schizophrenia may be associated with either an excess of dopamine or a hypersensitivity of dopaminergic receptors (see Chapter 11), it also has been hypothesized that some of the negative features of schizophrenia (such as apathy and withdrawal) may be the result of deficient neuronal activity in this medial frontal region (Pantelis et al., 1992). Finally, it is also interesting to note that selective lesions to the anterior cingulate gyrus have been found to be beneficial in relieving OCD symptoms (Ballantine, 1986).

From the foregoing discussion it is evident that while the different corticostriatocortical circuits utilize information from various sensory or posterior association areas, the thalamocortical radiations are invariably back to the frontal regions of the brain.[10] This organization suggests that these systems primarily are geared to impact on or modulate the execution of behavioral programs. As we shall see, this view is consistent with the current theories of the role of the basal ganglia on higher-order behavior.

Tables 6–3 and 6–4 summarize the major feedback loops that have been identified based on the different connections reviewed in the previous sections. Further speculations regarding the possible significance of several of these connections will be discussed following a review of some symptoms associated with lesions or dysfunction of this system. It should be kept in mind that the structures and connections listed here only offer a very broad, schematic representation of an exceedingly complex system. Each of the structures within the system has connections with structures lying outside the system, thus creating additional "open" circuits that can influence or be influenced by what takes place within these loops. Finally, refinements and/or additions to this schema can be expected in the future.

Table 6–3. Major Feedback Loops Involving Basal Ganglia Nuclei

1. **Cortical "direct" pathway**: Cerebral cortex → striatum → medial globus pallidus → thalamus → cerebral cortex[4]
2. **Cortical "indirect" pathway**: Cerebral cortex → striatum → lateral globus pallidus → subthalamus → medial globus pallidus → thalamus → cerebral cortex
3. **Cortical–nigral**: Cerebral cortex → striatum → substantia nigra → thalamus → cortex
4. **Midbrain**: Pedunculopontine nuclei → subthalamus → globus pallidus and substantia nigra → pedunculopontine nuclei
5. **Internal striatal**: Striatum → globus pallidus → thalamus → striatum
6. **Striatal–nigral**: Reciprocal, direct connections between the substantia nigra and the striatum
7. **Subthalamic**: Reciprocal, direct connections between the globus pallidus and the subthalamus

Table 6–4. Summary of Basal Ganglia – Cortical Feedback Loops

Circuit	*Cortical Origins*	*Striatal/Thalamic Projections*	*Possible Functional Roles*
Motor	Sensorimotor	Putamen/VA, VL	Modulate voluntary movements
Oculomotor	Visual eye fields	Caudate/VA, DM	Voluntary eye movements, visual search
Dorsolateral	Prefrontal? P-T	Caudate/VA, DM	Higher cognitive, executive functions
Lateral Orbito-frontal	Orbito-frontal, Ant. temporal	Caudate/VA, VM (ventral)	Emotional, instinctual drives and behavior
Limbic	Ant. cingulate, medial frontal, hippocampal	N.accumbens/DM	Drive, motivation

FUNCTIONAL CONSIDERATIONS

Having reviewed the better known structural associations of the basal ganglia, we might ask, "What are their clinical significance?" Before offering some speculations in this regard, it will be useful to review some of the more prominent symptoms and syndromes that have been classically linked with lesions of these nuclear masses and/or their pathways. It is to these that we now turn our attention.

Recognizing Disorders of the Basal Ganglia

Shortly after the turn of the century, S.A. Wilson described a disease that resulted from a genetic deficiency in copper metabolism. This disease, which is known as **hepatolenticular degeneration,** or *Wilson's disease*, was characterized by **muscle tremors**, **rigidity,** and **dystonia**. This disease was observed to first affect the liver and secondarily the brain. The lenticular nuclei, particularly the putamen, were most notably involved and Wilson was one of the first to use the term "*extrapyramidal*" in relation to the particular motor disturbances affecting the basal ganglia.

However, Wilson was not the first to identify a disease that was identified primarily with the basal ganglia. Almost 100 years earlier, James Parkinson had described a slowly progressive muscular disorder that bears his name. **Parkinson's disease**, which also is referred to as "*paralysis agitans*," is associated with degeneration of the substantia nigra (pars compacta), which results in **depletion of dopamine**. Parkinson's disease is clinically characterized by the tetrad of (1) a coarse **resting tremor** (particularly of the hands),

(2) **muscular rigidity** and **resistance to passive movement**, (3) **bradykinesia** (slowness of movement), and (4) **diminished postural reflexes**. Parkinson patients also commonly manifest a slow shuffling gait, masked faces (a flat, expressionless face), micrographia (small, cramped handwriting), and diminished volume and prosody (emotional intonation) of speech. Memory loss and depression, although not uncommon, are less consistently present, especially during the early and middle stages of the disease.

In the latter part of the 19th century, yet another physician, George Huntington, described a disorder that bears his name, **Huntington's chorea**. It was noted that Huntington's chorea tended to run in families (an autosomal dominant disorder with 100% penetrance) and was characterized by bizarre and dramatic choreiform movements and mental deterioration. The genetic defect subsequently identified as being linked with this disorder is an excessive number of CAG (cytosine–adenine–guanine) trinucleotide sequences (>35) on chromosome 4, resulting in a mutant form of the **huntingtin gene**, which is responsible for producing the huntingtin protein. The CAG sequence, in turn, is responsible for the production of the amino acid *glutamine* and inserting it into the huntingtin protein. Thus the excessive number of CAG sequences present in the gene results in an abnormally large huntingtin protein containing an excessively large amount of glutamine, which is thought likely to have a toxic effect on neurons, particularly the GABAergic spiny neurons of the caudate and putamen. Perhaps for this reason, Huntington's disease long has been thought to be associated with relative depletions of **GABA** (Bird et al., 1973; Perry, Hanson, & Kloster, 1973) and marked degeneration of the caudate nuclei. However, as will be noted in Chapter 11, changes in other neurotransmitters are likely also involved. The degeneration in the head of the caudate results in a flattening of the convexity of the anterior horns, a change that can be identified on CT or MRI scan (Figure 6–6). **Memory disorders** and other **mental and behavioral changes**, which commonly are associated with this disorder, may either antedate or develop subsequent to the **choreiform movements**. It should be noted that although subcortical basal ganglia structures primarily are involved in both Parkinson's and Huntington's diseases, other areas of the brain, including the cerebral cortex, are likely to be affected.

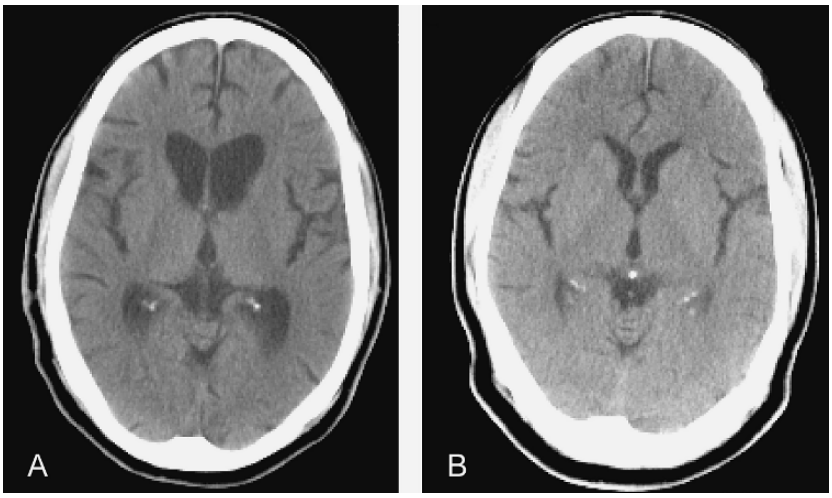

Figure 6–6. (a) Bilateral degeneration of the caudate nuclei in Huntington's disease. While some generalized cortical atrophy is present, compare the shape of the anterior horns of the lateral ventricles with that of (b) an age-matched control.

These and other acquired movement disorders (e.g., striatonigral degeneration, Sydenham's chorea, and hemiballismus) all have motor disturbances characterized by abnormal tone and/or involuntary movements due to involvement of the basal ganglia. These disorders commonly are referred to as diseases of the "extrapyramidal" motor system. This is because the basal ganglia were once thought to exert an influence on the peripheral musculature (or nervous system) that was somehow independent of the corticobulbar or corticospinal tracts or "pyramidal" system. However, as we have seen, these basal ganglia structures do not have a direct spinal pathway, but rather serve to modulate or influence cortical motor neurons that eventually give rise to the corticobulbar or corticospinal (pyramidal) tracts.

Specific Symptoms Associated with Disorders of the Basal Ganglia

Chorea (*choreiform movements*) refers to sudden, brief (although continuous over time) purposeless, unpredictable, involuntary jerks. These also have been described as "fragments of voluntary movements" and may involve the hands, limbs, trunk, or face. Although often bilateral, these abnormal movements may be restricted to one side of the body. Within these limits, the distribution of the jerking motions will be variable and apparently random. These abnormal movements are most commonly seen in Huntington's or Sydenham's chorea. In Sydenham's chorea the movements are more likely to be restricted to the limbs, whereas in **Huntington's disease**, the truncal musculature is more frequently involved.

Athetosis describes slow, irregular, writhing movements, predominately affecting the distal portions of the upper extremities, although more proximal muscles of the shoulders, hips, and trunk also can be involved. Athetosis of the facial muscles results in grimacing and abnormal movements of the tongue. Again these movements are involuntary and interfere with both active movement as well as the intention to keep a limb in a fixed position (at rest). This type of movement disorder appears to result from the simultaneous contraction of antagonistic muscles. Hypertonicity of the muscles is typically present. At times differentiation of chorea from athetosis is difficult. Elements of both might be simultaneously present and is referred to as **choreoathetosis**. Athetosis is commonly associated with **cerebral palsy** in which the basal ganglia, particularly the striatum, are affected.

Ballismus is a sudden, involuntary, "flinging" or throwing motion of an extremity. Although ballismus may involve both sides of the body, it more commonly is limited to one side of the body (*hemiballismus*) and typically is associated with lesions of the contralateral subthalamus. At times this disorder is thought to simply represent a particularly severe form of chorea.

Dystonia is characterized by a slow, sustained, or prolonged involuntary contraction of the trunk and proximal musculature, typically producing an abnormally contorted or "twisted" posture. Dystonia may result from multiple etiologies and again, either may be generalized or limited to certain, specific muscle groups. Examples of the latter include **spasmodic torticollis** or **blepharospasm** (a forceful closing of the eyelids). In some cases, the deformity may be limited to the distal portion of a single extremity. Hemidystonia may result from focal lesions (contralateral) of the striatum and/or thalamus.

Tremors may have multiple etiologies (some nonpathologic) and predominately may become manifest either at rest, in the performance of an action, or while maintaining a posture against gravity. The latter, for example, often are seen in cerebellar system lesions or chronic alcoholism. The type most commonly associated with basal ganglia disease is a **resting tremor** with a frequency of approximately 4 to 6 cps. Typically associated with **Parkinson's disease**, the tremor generally involves the fingers and wrists, often resembling a "pill-rolling" movement. This tremor typically disappears during intentional movements, although other disorders of movement might be seen (e.g., bradykinesia, rigidity, micrographia).

Table 6–5. Motor Symptoms Associated with Basal Ganglia Disease

Chorea:	Brief, purposeless, unpredictable, involuntary movements
Athetosis:	Slow, irregular, writhing movements, especially in distal upper extremities
Ballismus:	Sudden, involuntary, flinging or throwing motion of arm
Dystonia:	Slow sustained, involuntary contraction of trunk or proximal muscles
Resting tremor:	4 to 6 cps tremor while limb is at rest, most noticeable in fingers ("pill rolling") or hands
Rigidity:	Increased muscle tone, resistive to passive movement, either "lead pipe" (constant) or "cog-wheeling" (intermittent)
Bradykinesia:	Slowness in initiating or executing voluntary movement

Rigidity frequently is found in Parkinson-type syndromes and is manifested as increased muscle tone and resistance to passive movement. When the limb is passively moved, there may be evidence of rapidly alternating resistance and relaxation ("*cogwheeling*") or steady resistance throughout the range of motion ("*lead-pipe*" *rigidity*), the former being the more common. When rigidity is due to basal ganglia lesions, deep tendon reflexes (DTR) may be normal, which helps to differentiate rigidity resulting from basal ganglia disease from upper motor neuron spasticity that is associated with hyperactive DTRs and "clasp-knife" rigidity on passive manipulation of the limbs.

Bradykinesia is characterized by slowness in the initiation and/or execution of voluntary movement. There also may be a reduction in the number of movements manifested (*hypokinesia*). Such patients may have difficulty in initiating walking and may walk with a slow, short, shuffling gait without a normal swing to the arms. Since patients with bradykinesia are slow to make postural adjustments, balance may be compromised. The face of such individuals may show limited emotional expressiveness (masked face). Writing tends to be slow and micrographic and speech is typically monotonic and decreased in volume (hypophonic). Table 6–5 summarizes these various symptoms.

ETIOLOGY AND EFFECTS OF DISRUPTION OF NEUROCHEMICAL PATHWAYS

Multiple syndromes involving the basal ganglia have been identified. These can result from a variety of causes, including:

1. Birth defects (cerebral palsy).
2. Genetic defects (dystonia musculorum deformans, Huntington's disease).
3. Metabolic deficiencies (Wilson's disease).
4. Infectious or inflammatory disease (Sydenham's chorea).
5. Systemic disorders (systemic lupus erythematosus).
6. Drug toxicity (e.g., phenothiazines → Parkinson-type syndrome, overdose of L-dopa → choreoathetosis).
7. Neurodegenerative disease (Parkinson's).
8. Structural lesions (stroke, tumor).

Earlier in this chapter some of the well-known neurochemical pathways that interconnect the various nuclear components of the basal ganglia and interface with the thalamus and cortex were reviewed. As was suggested previously, our knowledge and appreciation of the complexity of these pathways and their clinical significance is still quite limited.

However, while recognizing these limitations, even a highly simplified outline of some of the neurochemical mechanisms purported to underlie several of the more classic basal ganglia disorders might add to a better understanding and appreciation of the symmetry of this system. Because the chemical mechanisms and pathways that subserve the motor symptoms have been studied in greater detail, these will serve as our model. Several of the more common and well-studied syndromes and/or symptoms associated with lesions to the basal ganglia, along with their suspected primary chemical mechanisms and pathways, are reviewed below.[11]

Parkinson's Disease

It has been well established that parkinsonism is related to a degeneration of cells in the pars compacta of the substantia nigra. This cell loss and neuronal pathology in the substantia nigra results in a depletion of the neurotransmitter dopamine (Hornykiewicz & Kish, 1987; Hirsch, Graybiel, & Agid, 1988). As was seen in Figure 6–3, dopaminergic pathways normally exert a major influence on the striatum and this influence can be either facilitatory or inhibitory, depending on the particular cells to which they project and the type of receptors employed (D_1 versus D_2). Recall that the "direct" striatothalamic pathways tend to have a disinhibitory (i.e., a facilitating) effect on thalamocortical projections and the opposite is true of the "indirect" pathway, which tends to inhibit thalamic neurons. If there is a reduction in dopamine to the striatal (caudate or putamen) cells that project to the medial segment of the pallidum as a result of diminished D_1 connections ("direct" pathway), these striatal cells will show reduced rates of firing since dopamine tends to exert an excitatory influence on them. Consequently, since the striatopallidal connections (GABAergic) are inhibitory, there will be less inhibitory influences on the cells of the medial segment of the globus pallidus (GPi), which means the firing rate of these GPi cells should increase. This, in turn, should result in an increase in the normal inhibitory influence of the GPi on the VA/VL nuclei of the thalamus. Since these thalamic nuclei are thought largely to exert a facilitatory influence on the cortex, that influence will be diminished, resulting in diminished cortical excitation (reduced motor activity of targeted agonist muscles?) (see also Chapter 11).

A comparable effect would be expected with a reduction of dopaminergic input to the striatal cells projecting to the external pallidal segment ("indirect" pathway), but for different reasons. Recall that earlier it was noted that the "indirect" striatothalamic pathways are thought normally to exert an inhibitory influence on antagonist muscles as a way of inhibiting unwanted motor activity. Since dopamine is thought to exert an inhibitory influence on this "indirect" system via D_2 receptors, this means that dopamine normally would have a modulating effect on this inhibitory system. Thus, if the supply of dopamine is reduced, as in Parkinson's disease, this would be expected to result in an enhancement of the inhibitory influence of the "indirect" pathway as the normal inhibitory dopaminergic influence on the D_2 receptors in the striatum is diminished. As can be seen from Figure 6–3, this would lead to an even greater *disinhibition* of the subthalamus and an increased facilitatory influence on the medial segment (GPi). This, in turn, again means that the GPi would tend to exert a greater inhibitory influence on the VA/VL nuclei, leading to decreased thalamic output (reduced cortical excitation).[12]

However, at first glance, there would appear to be at least one major obvious flaw in this scenario. As we saw above, given the differential effect that dopamine appears to have on the striatal neurons that contribute to the direct and indirect pathways, a depletion of dopamine should have the same end result for both the direct and indirect pathways, namely, reduced cortical activation. While the majority of the motor symptoms associated with Parkinson's disease indeed involve diminished motor activation [e.g., difficulty initiating movement (akinesia), slowness of movement (bradykinesia), decreased reflexes, "masked"

facial expressions, and decreased speech volume], signs suggestive of increased or overflow movements also are present (e.g., resting tremors and rigidity).[13] If the effect of dopamine depletion is to reduce cortical activation in both the direct and indirect pathways, how are we to explain the presence of tremors and the rigidity?

One potential explanation for this phenomenon hinges on the assumption that the various neurochemical transmitters contributing to the proper functioning of the cortical → basal ganglia → thalamic → cortical motor system normally are in a delicate balance. In the event of significant dopamine depletion this "balance" (whether between the direct and indirect pathways, the D_1 and D_2 receptors, or the interactions between dopamine and glutamate or between dopamine and acetylcholine) is disturbed. It is this imbalance that may contribute both to the hypokinetic and the hyperkinetic symptoms (see: Schmidt, 1995). In fact, it also has been suggested that the relative overactivity of glutamate may be as much if not more of a factor in producing symptoms in Parkinson's disease than dopamine depletion itself (Carlsson & Carlsson, 1990; Greenamyre, 1993; Starr, 1995; Lange, Kornhuber, & Riederer, 1997).[14] On the other hand, the fact that antimuscarinic (anticholinergic) drugs often are effective in reducing the tremors and rigidity in Parkinson's disease, suggests that a dopamine/cholinergic imbalance may be important in the development of these latter symptoms (recall that acetylcholine is an important interneuron neurotransmitter within the striatum).

There are additional unanswered questions with regard to Parkinson's and the model presented above (Obeso, Rodriguez, & DeLong, 1997). For example, the medial or internal segment of the globus pallidus tends to exert an inhibitory influence on the VA and VL nuclei of the thalamus. If these thalamic nuclei in turn tend to have a facilitatory influence on the motor cortex, then lesions to the internal segment of the globus pallidus, theoretically at least, should result in dyskinesias or overflow movements as a result of uninhibited thalamic output. At the same time, lesions affecting the thalamus might be expected to have a dampening effect on motor activity (i.e., produce bradykinesia or hypokinesia) as a result of diminished thalamic output. However, this is not what typically happens. While infarctions involving the basal ganglia (both the striatum and the globus pallidus) might result in a parkinson-type syndrome (Inzelberg, Bornstein, Reider, & Korczyn, 1994; Reider-Groswasser, Bornstein, & Korczyn, 1995), unilateral infarctions of the VA or VL (motor) nuclei of the thalamus rarely lead to permanent, severe motor deficits. To the contrary, therapeutically designed, stereotaxic pallidal lesions in Parkinson patients tend to relieve, rather than exacerbate some of the hyperkinetic symptoms of Parkinson's disease (e.g., tremors and rigidity). Lesions in the motor thalamus are even more effective in relieving these hyperkinetic symptoms without worsening the hypokinetic symptoms. In fact, some seem to improve in this respect, possibly as a result of reduced muscular rigidity.[15] Parenthetically, a newer, but more controversial, treatment approach to Parkinson's disease involves the transplantation of human embryonic cells from the pars compacta of the substantia nigra into the brains of Parkinson's patients. These transplanted cells provide a renewed, internal source of dopamine.

Additional Behavioral Effects of Dopamine Dysregulation

Parkinson's disease does not just affect the motor system. Affective disturbances along with other cognitive disturbances often coexist and in some cases a dementia-type syndrome may develop (Baev, 1995; Boller, 1980; Benson, 1984; Brown & Marsden, 1988, 1990; Cummings, 1988; Huber & Cummings, 1992; Gabrieli, 1995; Jacobs et al., 1997; Taylor et al, 1986). Recall that the basal ganglia have connections with most association cortices, especially the frontal lobes. Also, in addition to the more well-known nigrostriatal dopaminergic pathways, the ventral tegmental area (VTA) also provides strong dopaminergic links to the limbic and prefrontal areas. In turn, these areas also have links to the

basal ganglia (Cooper, Bloom, & Roth, 1991). Disturbances of these dopaminergic pathways and/or of neurotransmitters that directly or indirectly impact on dopamine have been implicated in various psychiatric conditions, most notably schizophrenia (Cooper, Bloom, & Roth, 1991; Crow, 1980; Gray et al., 1991; Haber & Fudge, 1998; Davis, Kahn, Ko & Davidson, 1991; Tassin, 1998). These findings have led to the development of the *dopamine hypothesis of schizophrenia* (see Box 6–1; Chapter 11). While this hypothesis is now recognized to be insufficient, in and of itself, to fully explain the etiology and symptoms of schizophrenia, it does provide some insights into how the basal ganglia and its neurotransmitters may impact on a range of mental disorders.

Box 6–1. Schizophrenia and the Dopamine Hypothesis

In the early 1950s chlorpromazine (Thorazine), being used as an antihistamine, was noted to have antipsychotic effects. It subsequently was discovered that Thorazine and related neuroleptics apparently had the capacity to block dopamine receptors, particularly mesolimbic D_2 receptors. It also was discovered that chronic use of these neuroleptics often led to the development of parkinsonian-type symptoms and conversely that antiparkinsonian drugs (as well as amphetamines and cocaine, which tend to increase dopamine availability) had a tendency to exacerbate psychotic symptoms. Additionally, there were reports of increased densities of D_2 receptors in certain parts of the basal ganglia in neuroloptic-free schizophrenic patients and elevated levels of homovanillic acid (a metabolite of dopamine) in the cingulate and frontal cortices of autopsied schizophrenic patients (Cooper, Bloom, & Roth, 1991). Findings such as these led to the assumption that schizophrenia was likely related to either an excess of dopamine or a supersensitivity of D_2 (and/or D_4) receptors to the presence of dopamine. While not discarding the importance of dopamine in the manifestation of schizophrenia, most researchers currently believe that the dynamics of schizophrenia are probably much more complex and likely involve numerous other neurotransmitter interactions. For example, many of the newer, "atypical" antipsychotics, such as clozapine (Clorazil) and risperidone (Risperdal) appear to exert antipsychotic effects through their ability to block serotonin receptors (Meltzer, 1990, 1991).

Despite the obvious complexity of these systems, it is interesting to speculate how changes in dopamine sensitivity might help account for schizophrenic symptoms. For example, if we apply the analogy of the motor systems (especially the indirect pathways discussed earlier) to the mesial frontal/limbic loops, it might be suggested that increased dopamine activity (sensitivity) at D_2 synaptic junctions may result in increased inhibition of the indirect (inhibitory) pathways. This subsequent "disinhibition" of the thalamocortical connections might then result in an overflow of sensory excitation (i.e., decreased filtering of irrelevant stimuli) and/or the inability to inhibit competing or intrusive thoughts, both of which may contribute to some of the positive symptoms of schizophrenia (hallucinations, delusions, distractibility, nonlinear thinking). Some of the "negative" symptoms of schizophrenia (apathy, flattened affect, and social withdrawal) have been associated with concomitant decreases in mesocortical dopaminergic pathways as a result of negative feedback loops (Davis et al., 1991), relative depletions of glutaminergic activity (Carlsson & Carlsson, 1990), or enhanced serotonergic activity (hence, the effectiveness of drugs like Clozaril). Finally, some of the side effects of the phenothiazines (e.g., tardive dyskinesia) are explained as probably resulting from the "supersensitivity" of D_2 receptors in the striatal motor pathways following chronic use of receptor blocking agents.

Huntington's Disease

As was noted earlier, Huntington's disease is associated with degeneration of the striatum. The pathological changes are most prominent in the head of the caudate and as noted earlier can be visualized by the loss of convexity in the anterior horns of the lateral ventricles (Figure 6–6). This degeneration leads to a dramatic loss of GABAergic fibers from the striatum to the external segment of the globus pallidus and to the substantia nigra. In many respects, the end result clinically is just the opposite of that seen in Parkinson's. If Parkinson's disease primarily can be characterized as an underarousal of the motor system or hypokinetic syndrome (e.g., bradykinesia, shuffling gait), Huntington's is marked by an overflow of movements or a *hyperkinetic* syndrome (chorea, athetosis, and ballismus). A review of the neurochemical pathways in Figure 6–3 reveals why this may be the case. If the GABAergic striatonigral pathways are generally inhibitory, the net effect of their loss is to have a disinhibitory effect on the substantia nigra. Being disinhibited, the substantia nigra thus is free to produce an excess of dopamine, which as we have just seen tends to lead to excessive motor output.

Likewise, if the normal inhibitory action of the striatopallidal fibers to the external segment (of globus pallidus) is lost or reduced, the normal inhibitory effect of the pallidosubthalamic fibers will be increased (since their cells of origin will be disinhibited). With the increased inhibition of the subthalamus, the excitatory influence it normally has on the medial portion of the globus pallidus will be reduced, resulting in turn in the diminished firing of the inhibitory pallidothalamic fibers. The now disinhibited thalamus is free to barrage the cortex with excitatory impulses, creating the potential for excessive motor output (i.e., overflow movements).

As will be discussed in greater detail in Chapter 11, increased dopamine has been associated with psychiatric disturbances, particularly schizophrenic-type illnesses. Huntington's is no exception. Frequently, although not invariably, this disorder is associated with marked behavioral disturbances early in the disease process, including blatant psychosis, paranoid delusions, and hallucinations (Dewhurst et al., 1969; Garron, 1973; Lishman, 1987; McHugh & Folstein, 1975; Shoulson, 1990). Mental or cognitive deterioration also can be encountered in the early stages of this disorder (Barr et al., 1978; Brandt, 1991; Butters et al, 1978; Caine et al., 1978). As in Parkinson's, some of these non-motor changes could be a reflection of more extensive, direct cerebral involvement, but the likelihood is that many if not most of these effects are produced via basal ganglia connections with non-motor association cortices, especially those associated with frontal and temporal–limbic systems.

Attempts to treat Huntington's commonly have involved trying to produce an increase in GABA in the CNS. However, oral administration of GABA compounds has been unsuccessful, since GABA does not readily cross the blood–brain barrier. Another way to increase CNS GABA would be to block dopamine receptors, but this means of treatment usually leads to other complications. Until more effective treatments are found, recent efforts have focused on identifying at-risk individuals before their childbearing years to reduce the expression of this disease through genetic counseling. However, the pros and cons of this approach have been debated because of the psychological impact of presymptomatic diagnosis on the at-risk individual.

Hemiballismus

Unlike Parkinson's and Huntington's, hemiballismus is a symptom rather than a disease or syndrome. Resulting primarily from a lesion affecting the subthalamus, hemiballismus can be produced by a variety of conditions, including Huntington's disease. Going back to our earlier diagram, what might we expect given a lesion affecting either the subthalamic fasciculus or the nucleus itself? In either case, the net result should be a reduction in

excitatory input to the medial pallidum via the subthalamic fasciculus. As was the case with Huntington's disease where the inhibitory pathways to the external pallidal segment were disrupted, the overall effect was to reduce the excitatory influence of the subthalamus on the inhibitory pallidothalamic fibers, producing a disinhibitory influence on the VA/VL thalamic nuclei. This in turn results in increased glutaminergic (excitatory) stimulation of the motor cortex, hence possibly creating the necessary environment for overflow phenomena such as involuntary ballistic movements. These mechanisms also help explain why such symptoms can present as part of the manifestations of Huntington's disease, as well as why overdoses of L-dopa also can lead to extraneous motor activity.

ROLE OF THE BASAL GANGLIA IN NORMAL BEHAVIOR

The preceding review focused primarily on motor symptoms associated with disturbances of the basal ganglia and was intended to offer some insight into the function of these subcortical nuclei. Although we now have reason to suspect that the basal ganglia also play an important role in a wide variety of cognitive and behavioral functions, the precise role of the basal ganglia nuclei in these latter areas are not clear. Nonetheless, it may be useful to review what we know, or at least suspect, about the role of the basal ganglia in both motor and non-motor behaviors.

Motor Behavior

One of the first questions to ask is whether as a group the basal ganglia (i.e., the caudate, putamen, globus pallidus, subthalamus, and substantia nigra) have **a** role or do they subserve **multiple** roles in the overall scheme of the central nervous system? Another way of phrasing the question may be to ask whether the sum of the activity of the basal ganglia is ultimately directed to the execution of motor response programs or are they also responsible for cognitive and emotional activities independent of specific motor activities? While it might be desirable to discover a single rubric under which all the activities of the basal ganglia could be subsumed, this goal is not likely to be fulfilled in the near future. For now, the best we may be able to do is to search for pieces of the puzzle.

Perhaps the logical place to start is in the area of motor activity: "*What role do the basal ganglia play with regard to motor behavior?*" First, most authors seem to agree that the basal ganglia probably are not primarily responsible for formulating or initiating motor responses (that being primarily the role of the prefrontal and agranular frontal cortices; see Chapter 9). However, the basal ganglia would appear to have the potential to facilitate the activation of some motor responses, while at the same time having an inhibitory influence on others. Most investigators seem to agree that the basal ganglia likely play a role in the following aspects of motor behavior:

1. Preparation for specific motor responses.
2. Smooth transitioning from one motor response to another.
3. Inhibiting movements or sets of actions that might interfere with the proper execution of the primary intended action.
4. Monitoring the direction, speed and amplitude of movements as a means of preparing for the next movement.
5. Initially learning and, later, smoothly executing series or patterns of movements
6. Possibly adapting to the internal and external (environmental) demands being placed on the organism and/or comparing planned or intended actions with outcome.[16]

Table 6–6. Comparison of Symptoms of Cerebellum vs Basal Ganglia Disease

Cerebellum	*Basal Ganglia*
Loss of balance/equilibrium	Slowness of movement
Ataxia/Asynergy	Chorea/athetosis/ballismus
Intention tremors	Resting tremors
Hypotonia	Hypertonia/rigidity

So how does all this translate into everyday motor activities? A useful model might be that of driving a car. Assume you are driving along the interstate. You are in a relaxed mood, singing along with the radio, or indulging in your "fantasy de jour" as you drive. Almost unconsciously you are making occasional, minor adjustments in your steering to stay in your lane, perhaps even negotiating gentle curves in the road without giving them any thought. At this point, connections between the visual system and the frontal agranular cortices are clearly operative, as is the cerebellum (as witnessed by the smooth, delicate movements of the steering wheel). What may be less apparent is the role played by the basal ganglia under these circumstances.[17] However, suppose that suddenly the car in front of you begins to behave erratically. Your singing or fantasizing stops abruptly, your posture becomes more erect, your grip on the steering wheel tightens slightly, and you become conscious of the brake pedal, even though you may not immediately take your foot off the accelerator. You are preparing for the possibility of having to make rapid adjustments in your motor response based on a change in external events and your own internal state of apprehension. You have inhibited certain potentially distracting activities (singing or daydreaming) and are ready to facilitate others (applying the brake, making a defensive steering maneuver). It is these actions and preparations for further actions based on situational demands that likely require substantial involvement of the basal ganglia. If you become too tense (freeze up) or remain too relaxed, you may not be able to respond in an optimal manner. It is these preparations or setting the tone for possible actions that may represent contributions of the cortical–basal ganglia interactions.

In summary, the basal ganglia probably are important in the *planning* and *preparation* of an action. They facilitate responses of the organism by setting the stage for the initiation and execution of a given action.[18] The fact that overflow movements (e.g., resting tremors, chorea, athetosis, and rigidity) also are a frequent accompaniment to basal ganglia disorders suggests that one way the basal ganglia might prepare for action is by selectively inhibiting or modulating muscular tone or activity that is inappropriate to carrying out the target action. In contrast, the cerebellum may be responsible for the actual smooth execution of the action once it has been initiated. Deficits resulting from cerebellar lesions generally are observed only during the process of trying to carry out a complex motor activity (e.g., maintaining one's balance when walking or a smooth rhythm while writing). At the same time, there appears to be certain areas of functional overlap between the cerebellum and the basal ganglia. For example, both seem to play a part in maintaining what Luria (1966) described as the "kinetic melody" of a motor response (i.e., the fact that each segment or part of the action flows smoothly and orderly, without hesitation or delay, from the previous segment). Either cerebellar or basal ganglia lesions can disturb this "kinetic melody."

The key concepts to remember here are *parallel processing* and *modulation*. Both are consistent with the notions of feedback loops discussed earlier. It is useful to keep in mind that the cortex, basal ganglia, cerebellum, as well as a few other brainstem structures (such

as the pedunculopontine nuclei, the red nuclei, and the inferior olivary nuclei) are all components of the motor system and act in concert with one another. Disruptions in more than one location at times may produce functional disturbances that may appear very similar. In their excellent review of some of these studies, Marsden and Obeso (1994) conclude that two of the more likely roles of the basal ganglia are to:

1. Monitor and facilitate the sequencing of cortically initiated motor responses by facilitating target or agonist actions and exercising an inhibitory influence on conflicting or "unwanted motor activity."
2. Interrupt (e.g., exert inhibitory influences and/or cease facilitating) activities that may no longer be appropriate given changes in either the internal or external milieu.

Non-Motor Behavior

The next question is, "*What role do the basal ganglia play with regard to emotional control, cognition, or other "higher cortical functions?*" Two general sources of anatomical evidence were reviewed earlier that suggest that the basal ganglia have much broader roles than simply ensuring that there is a smooth transition from one motor component to the next when executing a movement. One bit of evidence supporting the role of the basal ganglia in higher cortical functions is the fact that the parietal and temporal association cortices provide substantial input into the striatum. Other compelling evidence is the discovery of the dorsolateral, lateral orbitofrontal, and medial frontal circuits, which for the most part originate and project back to these cortical regions after converging on basal ganglia structures. These pathways, which were reviewed above, are generally associated with higher-level integrative and executive abilities, including the control of emotions, motivations, or drive states. Additional evidence touched upon earlier was the fact that in certain disease states (e.g., Parkinson's, Huntington's), various cognitive and affective disturbances frequently are reported. Some common psychiatric disorders, such as mood disturbances (Mayberg, 1994; Mayberg et al., 1988; Starkstein et al., 1987), schizophrenia, obsessive–compulsive, and other stress-related disorders, also have been linked with disturbances of the basal ganglia and related systems (Horger & Roth, 1996; Mega & Cummings, 1994; Swerdlow, 1995; Miguel, Rauch, & Leckman, 1997; Saint-Cyr et al., 1995; Zald & Kim, 1996a,b; Saxena, Brody, Schwartz, & Baxter, 1998). Discrete lesions of basal ganglia nuclei, as well as of those thalamic nuclei that constitute an integral part of the cortical–basal ganglia circuits described above, also have been associated with specific cognitive deficits such as aphasia (Robin & Schienberg, 1990; Damasio et al., 1982). Finally, in clinical practice it is not uncommon to find problems in learning or memory, visual–spatial skills, or higher-order "executive" functions in patients who have suffered lacunar infarcts involving the basal ganglia, although damage to nearby association or projection pathways also may contribute to the observed deficits (Alexander et al., 1987; Cappa et al., 1983; Naeser et al., 1982).

As described above, in addition to exerting some type of modulating influence with regard to sensorimotor activities, it would appear that the basal ganglia also perform a comparable function in relation to the cognitive and affective activities of the brain. Through the motor, oculomotor, dorsolateral, orbitofrontal, and cingulate "circuits" outlined earlier, the basal ganglia are not only in a unique position to integrate motor and sensory input with regard to motor activities, but also to integrate sensory input and its emotional valence, along with internally generated drive states to influence the executive command centers of the frontal lobes. As part of these latter "circuits," critically placed lesions within the basal ganglia may induce deficits comparable to cortical lesions involving these same circuits, that is, frontal, anterior cingulate lesions. In general, this is what frequently has been found. As

Table 6–7. Cortical versus Subcortical Dementia (Early Stages)

Dimension	*Cortical dementia*	*Subcortical dementia*
Physical appearance	Typically robust, physically active	Weak, more sedentary, stooped posture
Motor system	Generally no change	Major change: Tremors, dyskinesia, chorea, gait disturbances
Response speed	Normal, except perhaps when difficulties are encountered	More commonly slowed, even when response is correct
Speech	Good articulation, generally fluent	Dysarthric, slowed, occasionally hypophonic
Writing	Graphically intact, spelling, paraphasic errors	Dysgraphic (motorically), spelling or paraphasic errors are more rare
Language	Word finding diff., paraphasic errors, difficulty comprehending complex commands	(?)Slow to respond, but expressive and receptive language grossly intact
Memory	Difficulty learning, delayed recall poor, cuing or recognition may be of little help	Slow learning, esp. if active strategy involved, weak delayed recall, cue or recognition helpful
Cognition	Attention may be good, impaired problem solving, abstraction (not aided by extra time; perceptual, construction difficulties (due to V-S integration deficits)	Attention inconsistent, slow to problem solve, improves if given extra time, perception intact, construction impaired due to graphic problems, poor planning or impulsivity
Affect	Normal to mildly anxious or irritable	More likely to appear depressed, apathetic
Personality	Usually little change	May appear more disinhibited, inappropriate
Insight	Normal to mildly impaired (early only)	More likely to show change; indifference

Note: Not all symptoms will be present in all patients, especially in the earlier stages of either type of dementia process.

is the case with frontal cortical lesions, bilateral insults, although more rare, tend to produce more dramatic results.

Probably the blatant manifestation of these influences finds its expression in what has been termed the *subcortical dementias* (Albert et al., 1974; Cummings, 1990). Although the etiology of this general syndrome can be quite varied (for review, see Cummings, 1990) and may involve numerous subcortical structures, as well as the cortex itself, lesions affecting the basal ganglia and/or adjacent white matter pathways is common to most of these conditions. Huntington's disease, which was described earlier, is a quintessential example of this type of dementia in which there is early, bilateral involvement of the caudate nuclei, along with motor, behavioral, and cognitive symptoms. Because of their extensive connections with the frontal lobes (dorsolateral, orbitofrontal, and cingulate circuits), most of the "subcortical dementias" that typically impact these cortical → basal ganglia → thalamic → cortical pathways share many of the features of "frontal dementias" (Gustafson, 1987; Neary et al., 1988). Thus, in addition to symptoms of motor or "physical" disability, such patients commonly will manifest personality or behavioral changes (e.g., apathy, lability, and disinhibition) and cognitive changes more suggestive of "cognitive stickiness" (e.g., bradyphrenia, difficulty shifting mental sets, impaired concentration, and difficulty

retrieving information). Such symptoms may be contrasted to the more frank cognitive lacunae (e.g., aphasias or agnosias) commonly observed in the more posterior cortical dementias, such as Alzheimer's.[19] Table 6–7 presents some of the more common features that may help distinguish a predominately cortical dementia from a dementia in which there is early and substantial subcortical pathology.

Even though our understanding of the role of the basal ganglia in either motor or cognitive/emotional behaviors is still incomplete, it is nonetheless important to appreciate the complexity and range of their connections (both cortical and subcortical), as well as the range of behavioral disturbances associated with lesions affecting them. Such knowledge forces us to think not only in terms of specific nuclei, lobes, or structures, but also in terms of *cerebral systems*. Recognizing that the basal ganglia (as well as other structures) are part of larger functional systems, we learn to ask, "*How does a disruption of this nucleus impact on the larger functional system of which it is a part, and how does that differ from disturbances to other parts of this functional system?*" As we begin to think in this manner, we come closer to understanding how the brain is most likely organized and how it operates.

Endnotes

1. The *extrapyramidal* nature of these motor influences is now in question, as is the exclusive "motor function" of these nuclei.
2. As will be discussed, these areas are thought to represent ventral extensions of the putamen and globus pallidus, respectively, and appear to represent important connections to limbic structures, and hence, may play an important role in affect and neuropsychiatric behaviors.
3. Although the tail of the caudate nucleus terminates in the vicinity of the amygdala, a structure more closely associated with the olfactory system and other "limbic" structures, no direct connections are known to exist between the two (however, as will be seen, indirect connections may exist via the ventral striatum). The claustrum, a narrow band of gray matter lying between the putamen and the insular cortex and separated from them by the external and extreme capsules, respectively, is known to have reciprocal connections to the cortex, particularly the posterior or sensory cortices, but its functional significance remains obscure.
4. As one joke goes, "*How are the basal ganglia and a college dean alike?*" The answer is: "*Both take up a lot of space, but no one seems to know exactly what it is that they do*."
5. This includes the bed nuclei of the stria terminalis lying ventrolateral to the anterior horns of the lateral ventricles.
6. In addition to GABA, the striatopallidal fibers destined for the internal segment contain the peptide, substance P, while those projecting to the external segment contain enkaphalin. Also, while most of the neuronal fibers exiting the striatum are GABAergic and inhibitory, those that remain as internal association fibers (striatal interneurons) are largely cholinergic and excitatory.
7. Although the "direct" and "indirect" pathways are described here in relation to motor functions, recall that the neostriatum, especially the caudate nucleus, receives projections from widespread areas of the cortex. Thus, similar patterns of facilitation or relative inhibition also may influence cognitive and perceptual activities. Likewise, as will be seen, selective disruptions of specific aspects of these systems may help account for some of the symptoms seen in certain disease states (e.g., the rigidity in Parkinson's disease; the involuntary, "overflow" movements in Huntington's disease; or possibly even the difficulty in filtering out irrelevant, extraneous thoughts or stimuli).

8. The pedunculopontine nucleus is located in the area of the decussation of the superior cerebellar peduncles, which is a particularly crucial location for involvement in a motor feedback loop. In this location, the pedunculopontine nucleus has access to input from the motor cortex, globus pallidus, substantia nigra, and the cerebellorubrothalamic pathway.
9. Given what we know about the afferent and efferent connections between these various cortical areas, particularly the anterior cingulate gyrus, one might speculate that other thalamic nuclei also might be involved in these circuits.
10. While it is possible that feedback loops project back to the posterior association cortices, so far none apparently have been identified.
11. For reviews of the chemical pathophysiology and additional syndromes associated with lesions of the basal ganglia, see: DeLong (1990); McDowell and Cedarbaum (1991); Weiner and Lang (1989); Wichmann and DeLong, (1993).
12. Given these relationships, the opposite situation (i.e., increased dopaminergic activity) should result in increased cortical activation or arousal. In fact, this is what seems to occur with the administration of dopamine agonists, such as amphetamines.
13. Miyawaki, Meah, and Koller (1997) suggest that parkinsonian tremors may be associated with changes in serotonin levels.
14. Lesions of the subthalamic nuclei in experimentally induced parkinsonism in monkeys improved the symptoms of tremor and rigidity in these animals; this was taken as an indication that these "indirect" pathways were critical to the development of these hyperkinetic-type symptoms (DeLong, 1990). What makes this finding even more interesting is that, as previously noted, lesions of this nucleus in normal persons commonly produces overflow symptoms (e.g., hemiballismus).
15. See Marsden and Obeso (1994) for a more detailed review and explanations for these findings.
16. For additional reviews of proposed functions of the basal ganglia, see Albin, Young, and Penny (1989); Alheld, Heimer, and Switzer (1990); Ciba Foundation (1984); Cote and Crutcher (1991); DeLong (1990); DeLong and Georgopoulos (1981); Denny-Brown (1962); Gunilla, Oberg, and Divac (1981); Marsden (1987); Yahr (1976).
17. The roles played by the basal ganglia versus the cerebellum in such routine movements is not always well differentiated. Certainly some of the functions normally attributed to the basal ganglia (e.g., ensuring smooth transitions from one movement to another) also would seem to describe the operation of the cerebellum. Clinically, how do they differ? While some of the differences in the symptoms manifested by the two are presented in Table 6–6, there may be a more fundamental way of viewing this problem, which has to do with learning. To stick with this same analogy, think back to when you first learned to drive. Chances are, even though the road may have been straight and unobstructed, you likely were making constant and excessive excursions of the steering wheel, a process that required your full and undivided attention. However, as you became more accustomed to driving, the steering adjustments became much more refined and you were able to relax, perhaps now more easily dividing your attention between the road and finding a better station on the radio. During the initial learning phase, a much more conscious process, the basal ganglia probably were much more important in the planning, preparation, and execution of these skills. However, with practice, normal driving rapidly became much more automatic. Under these circumstances, many of the routine movements or adjustments more easily could be controlled by the cerebellum (i.e., they became less coarse and more precise). Thus, while the basal ganglia probably continue to be important in maintaining overall muscular tone, the facilitation and inhibition of agonist and antagonist muscle groups and the

initiation and sequencing of individual muscle groups (especially when executing highly specific, fully conscious, goal-directed activities), the cerebellum can assume considerable control over those overlearned, repetitive elements that have become largely automatic (Passingham, 1993). However, both patients with cerebellar and basal ganglia disturbances can show deterioration in carrying out skilled tasks that require a fluid transition between one element and the next.

18. Increased electrical activity can be detected in the basal ganglia just prior to the initiation of an action, and as has been noted certain disease states (e.g., Parkinson's) are characterized by difficulty initiating (and occasionally stopping) movements.
19. While Alzheimer's patients also may manifest "frontal" signs, they usually occur somewhat later in the disease process.

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