frontal eye field [59, 574] and limbic areas [75].

The inferior and lateral nuclei of the pulvinar receive important projections from the superficial layers of the superior colliculus and the pretectum. Projections from the deep, non-visual layers of the superior colliculus terminate in the medial pulvinar [102, 104, 572, 829, 1390]. Direct connections from the retina to the inferior pulvinar have been described [500].

The extrageniculate pathway from the superior colliculus via the inferior and lateral pulvinar to the visual association areas is responsible for residual visual discrimination after lesions of the striate cortex, as has been demonstrated both in experimental animals and in humans [226, 1217, 1490].

Connections of the Intralaminar Nuclei

The intralaminar nuclei are characterised by double projections, a diffuse projection to the cortex and a projection to the striatum. The striatal projection was first demonstrated in human material [1453] and later in experimental animals [313, 314, 990, 1100, 1101]. In cats, both the anterior and posterior group of intralaminar nuclei project to the entire striatum in an overlapping fashion [91, 616, 881, 1161]. The cortical projections of the intralaminar nuclei are diffuse, but are still concentrated in certain areas [508, 637]. A few cells within the intralaminar nuclei give rise to branching axons which terminate both in the cortex and the striatum [835, 1200]. The thalamocortical connections of the intralaminar nuclei are reciprocated by corticothalamic projections. The prefrontal cortex, cingulate gyrus and premotor area are connected with the anterior group of intralaminar nuclei. The motor and parietal cortices project to the centromedian and central lateral nuclei. There are fewer connections with the occipital and temporal lobes [642, 734, 736, 835, 881, 1076].

The main afferents of the intralaminar nuclei come from the spinothalamic and lateral trigeminothalamic tracts, the cerebellum and the globus pallidus. These connections are described in other chapters. The projections from the globus pallidus chiefly involve the centromedian and parafascicular nuclei [62, 338, 891, 1054]. The cerebellar and spinothalamic afferents terminate more rostrally, in the central, lateral and more rostral intralaminar nuclei [188, 263, 852, 935]. Fibres from the bulbar reticular formation, which have been claimed to enforce the diffuse spinothalamic projection to the intralaminar nuclei [134], do not appear to be very numerous [886]. The mesencephalic reticular formation, including the cuneiform nucleus, gives rise to an important projection to the intralaminar nuclei [152, 321].

Motor Systems

Long Corticofugal Pathways

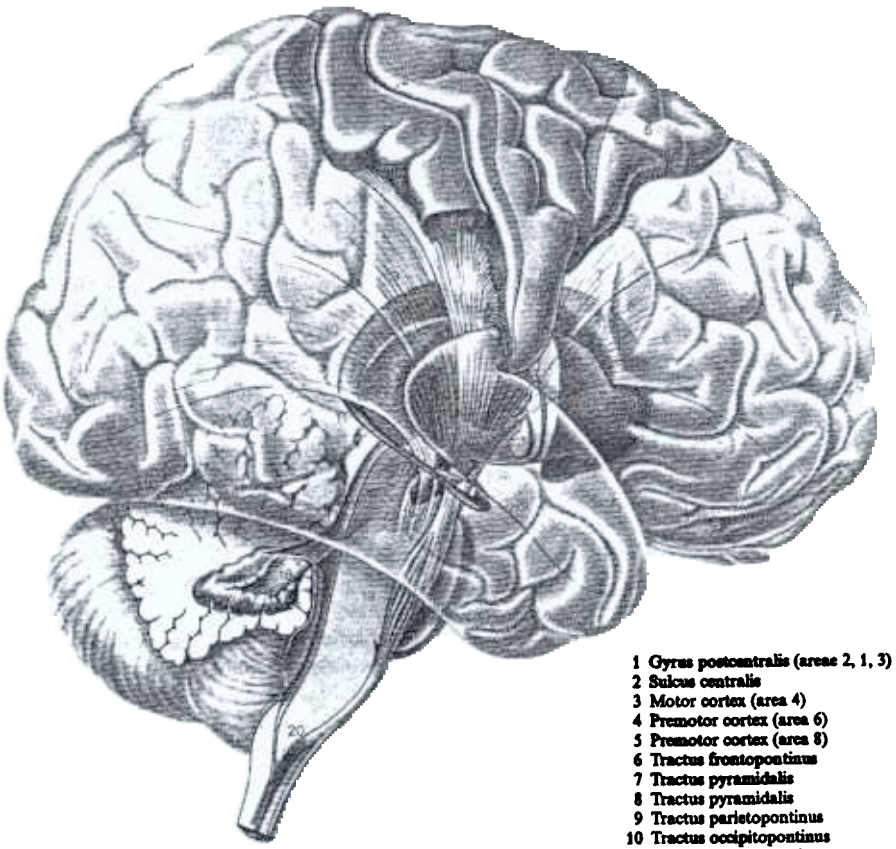
Introduction

Projection fibres from deep pyramidal cell layers of the cerebral cortex (cortical layers V and VI; [16, 114, 221, 222, 223, 363, 641, 665, 667, 668, 671, 672, 778, 826, 1277, 1519, 1523]) terminate in an orderly manner in the striatum, thalamus, brain stem and spinal cord. In the depths of the hemisphere these fibres constitute, together with the thalamocortical fibres, the corona radiata and the internal capsule (Fig. 170). Caudal to the optic tract they come to lie on the ventral surface of the brain stem as the cerebral peduncle. Most of the fibres of the cerebral peduncle are thin, but its middle division is distinguished by its content of thicker myelinated fibres. About 10% of these fibres are over 4 μm in diameter, the thickest fibres reaching a calibre of 20 μm [761, 1444].

After having passed the cerebral peduncle the corticofugal fibres enter the pons and split in smaller bundles. The medial and lateral corticopontine divisions of the cerebral peduncle terminate on the pontine nuclei, and the middle division of the peduncle continues, caudal to the pons, as the pyramidal tract (Fig. 174). The majority of the pyramidal tract fibres decussates at the bulbospinal junction to descend in the dorsolateral funiculus of the cord as the lateral pyramidal tract. A varying proportion of the fibres of the pyramidal tract does not decussate, but descends in the wall of the anterior fissure of the cord as the anterior pyramidal tract to midthoracic levels.

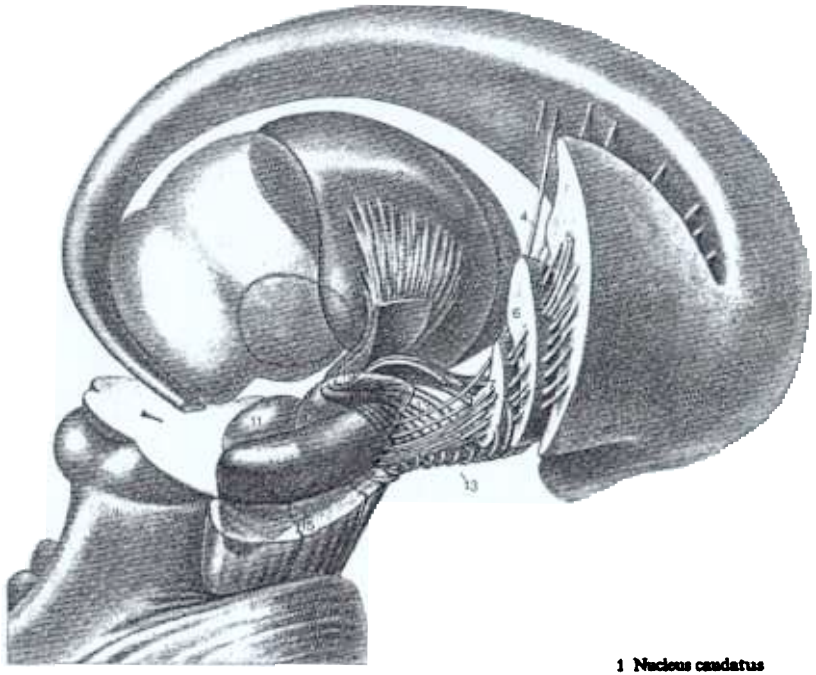
The majority of the fibres of the pyramidal tract take their origin from the motor cortex (area 4; [176]) and caudal premotor cortex (area 6), but 20% stem from the somatosensory and parietal cortices [609, 1408, 1409]. The largest fibres of the pyramidal tract are the axons of the giant pyramidal cells (or Betz's cells) in the motor cortex. In primates they constitute the fastest fibres of the pyramidal tract, which terminate directly on the motoneurons [1085, 1086]. The fibres from the somatosensory cortex terminate on relay nuclei in long ascending sensory pathways, including the ventral posterior thalamic nucleus, the nucleus princeps of the trigeminal nerve, the dorsal funiculus nuclei, the spinal nucleus of the trigeminal nerve and the dorsal horn (see Fig. 134 and the section on general sensory systems and taste). The fibres from the medial, frontopontine division of the cerebral peduncle take their origin from the premotor and prefrontal cortex [734, 1508]. The lateral division of the cerebral peduncle contains fibres from the parietal association cortex, with smaller contributions from the temporal and occipital lobes [673, 761].

During their course along the brainstem and the cord many fibres detach from the long corticofugal system, some as collaterals of ongoing fibres. Fibres to the pretectum and the superior colliculus leave the internal capsule, to course through the dorsal thalamus. Other fibres to the tegmentum and the tectum mesencephali leave the cerebral peduncle to pass through or along the substantia nigra. An important contingent of fibres detaches from the middle division of the cerebral peduncle and can be followed caudally through the area of the medial lemniscus



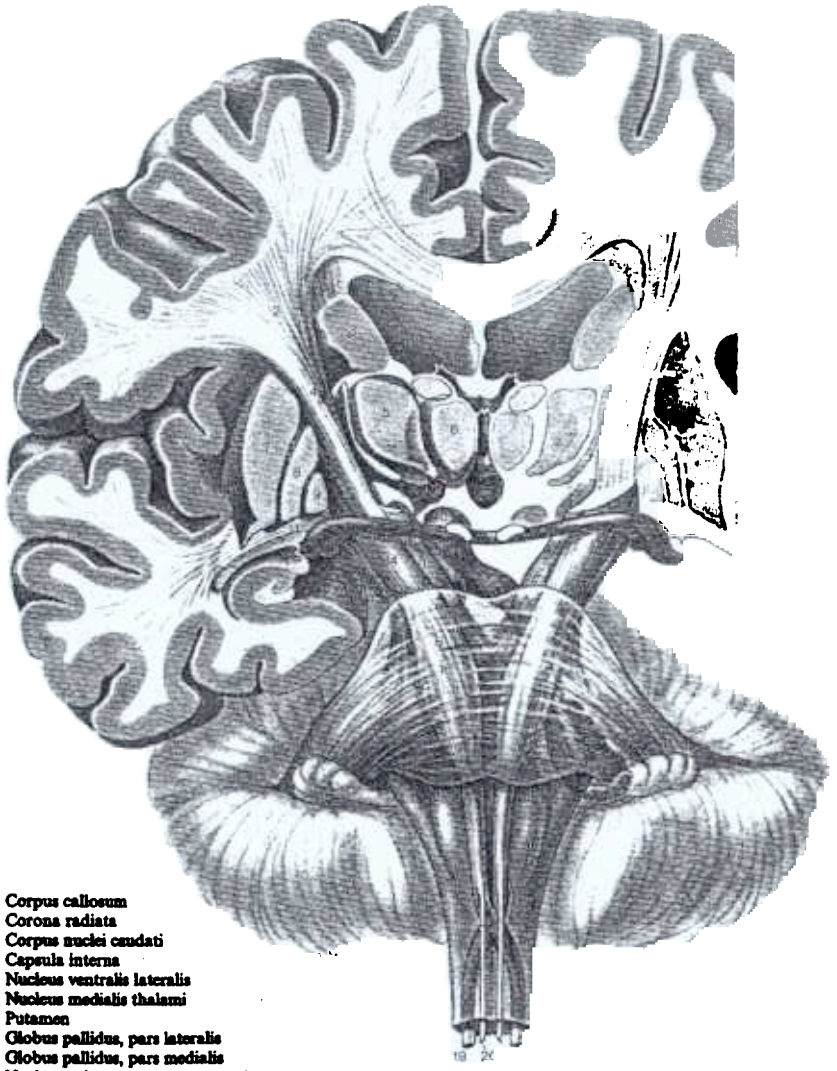
1 Gyrus postcentralis (areae 2, 1, 3)
2 Sulcus centralis
3 Motor cortex (area 4)
4 Premotor cortex (area 6)
5 Premotor cortex (area 8)
6 Tractus frontopontinus
7 Tractus pyramidalis
8 Tractus pyramidalis
9 Tractus parietopontinus
10 Tractus occipitopontinus
11 Cauda nuclei caudati
12 Caput nuclei caudati
13 Putamen
14 Globus pallidus
15 Substantia nigra
16 Tractus temporopontinus
17 Nucleus dentatus sinister
18 Pedunculus cerebellaris superior
19 Pons
20 Decussatio pyramidum

Fig. 170. Pictorial survey of the origin of the pyramidal tract in the cerebral cortex and of the long corticofugal system in a lateral view (1/1 ×). The brain stem and the cerebellum have been cut in the median plane and the right half has been removed, with the exception of the pyramidal tract



1 Nucleus caudatus
2 Nucleus ventralis lateralis
3 Fasciculus thalamicus
4 Fibrae strionigrales
5 Putamen
6 Globus pallidus, pars lateralis
7 Globus pallidus, pars medialis
8 Fasciculus lenticularis
9 Nucleus reticularis thalami
10 Zona incerta
11 Nucleus ruber
12 Nucleus subthalamicus
13 Ansa lenticularis
14 Substantia nigra
15 Pedunculus cerebri
16 Pons

Fig. 171. The nuclei and fibre bundles of the so-called extrapyramidal system in a lateral view (12/5 ×). Of the fibres originating from the occipital, removed part of the lentiform nucleus, only the ansa lenticularis is represented



1 Corpus callosum
2 Corona radiata
3 Corpus nuclei caudati
4 Capsula interna
5 Nucleus ventralis lateralis
6 Nucleus medialis thalami
7 Putamen
8 Globus pallidus, pars lateralis
9 Globus pallidus, pars medialis
10 Nucleus ruber
11 Capsula interna, pars retrolentiformis
12 Cauda nuclei caudati
13 Tractus temporopontinus } Pedunculus cerebri
14 Tractus pyramidalis } Pedunculus cerebri
15 Tractus frontopontinus } Pedunculus cerebri
16 Pons
17 Pyramis
18 Decussatio pyramidum
19 Tractus pyramidalis lateralis
20 Tractus pyramidalis anterior

Fig. 172. The long corticofugal fibre system in a frontal view (6/5×). The plane of the section shown in this figure coincides with the long axis of the brain stem

1 Corona radiata
2 Corpus nuclei caudati
3 Putamen
4 Fibrae strionigrales
5 Capsula interna, crus posterius
6 Nucleus reticularis thalami
7 Nucleus centromedianus
8 Fasciculus thalamicus
9 Zona incerta
10 Fasciculus lenticularis
11 Nucleus subthalamicus
12 Substantia nigra
13 Nucleus parafascicularis
14 Ansa lenticularis
15 Nucleus ruber
16 Tractus opticus
17 Capsula interna, pars sublentiformis
18 Cauda nuclei caudati
19 Pedunculus cerebri
20 Pons

Fig. 173. The nuclei and fibres of the so-called extrapyramidal system in a frontal view (12/5×). The fibres originating from the removed frontal part of the lentiform nucleus are not illustrated with the exception of the ansa lenticularis. The plane of the section is the same as in Figure 172

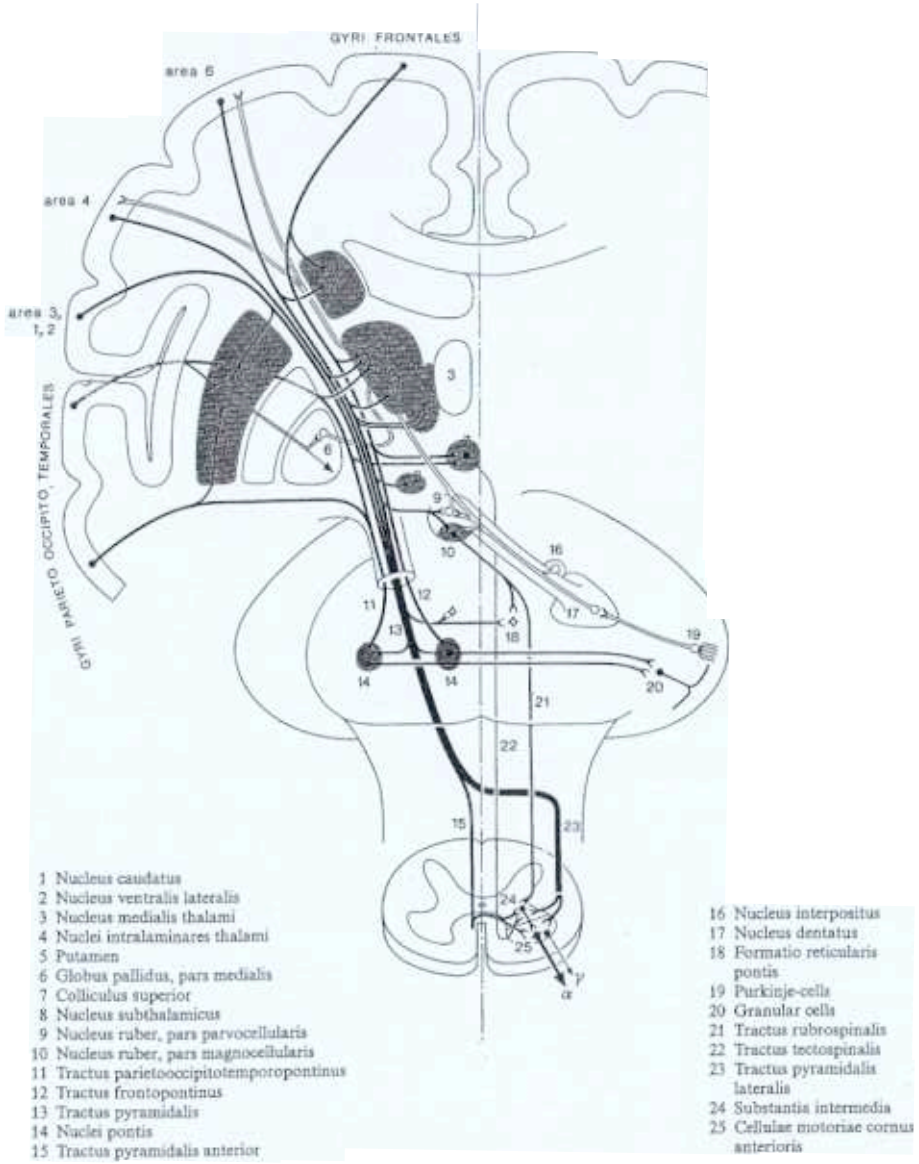


Fig. 174. The neuronal connections of the pyramidal system. Feedback pathways are in *open contour*.

[761] where it enters the medial reticular formation or rejoins the pyramidal tract [744]. Corticobulbar fibres detach from the bundles in the pons and the pyramid. The corticofugal system presents many species variations in the level of its major decussation, in its localization, and in the extent of its descent in the spinal cord [1443]. In humans interindividual variations are present with respect to the completeness of the pyramidal decussation, which on occassion may have failed to develop [822, 1442] and to the occurrence of aberrant fascicles, such as the circumolivary bundle, which detaches from the pyramid and turns back to terminate on the pontobulbar body [1319].

Medial and Lateral Motor Systems

The main terminations of the long corticofugal system in the brain stem and spinal cord include the tectum, the basal pontine nuclei, the reticular formation and the intermediate zone of the spinal cord, the somatosensory relay nuclei and the motor nuclei. Most of these cortical connections are mentioned in the chapters on the somatosensory system, the special sensory systems and the cerebellum. The direct and indirect cortical projections through interneurons and brain stem pathways to the motor nuclei of the brain stem and the spinal cord were extensively studied and summarized by Kuypers [744, 745]. His concept, according to which the motor system can be subdivided into separate medial and lateral systems is based on the organization of the motoneuronal cell groups, their interneurons and the descending pathways (Fig. 175).

The lateral system (Fig. 175A) includes the lateral motor column of the spinal cord, namely the motoneurons innervating distal muscles of the limbs [364, 1142, 1296] and several somatomotor cranial nerve nuclei, in particular the ventral (in lower mammals lateral) part of the facial nucleus, which innervates the perioral muscles [260, 738]. Interneurons innervating lateral motoneurons are located in the dorsolateral part of the intermediate zone of the cord and the lateral part of the lateral (parvocellular) reticular formation of the medulla oblongata and the pons. The axons of these lateral interneurons are generally short. In the cord they are located a few segments rostral to their termination in the ipsilateral anterior horn. Interneurons projecting to the ipsilateral ventral part of the facial nucleus are located in the medulla oblongata, with those projecting to the ipsilateral hypoglossal nucleus more caudally, and those projecting bilaterally to the motor nucleus of the trigeminal nerve more rostrally in the lateral reticular formation.

Descending fibres of the rubrobulbar and rubrospinal tract from the contralateral red nucleus terminate on interneurons in the lateral reticular formation and the dorsolateral intermediate zone of the spinal cord and directly on motoneurons of the nucleus of the facial nerve and, in the cat, on a small motoneuronal cell group in the dorsolateral part of the anterior horn at C8 and T1 [533]. The rubrobulbar and rubrospinal tract is somatotopically organized. Cells projecting to the facial nerve nucleus occupy the dorsal part of the red nucleus, and the cells projecting to the cervical and lumbar enlargements are located in its intermediate and ventrolateral parts respectively [544, 1013, 1092]. Rubrospinal fibres which distribute branches to both enlargements are few [576, 1239]. The rubrospinal system has an excitatory influence on contralateral flexor motoneurons and inhibits contralateral extensors [546, 547, 1198]. Lesions of the rubrospinal tract result in motor deficits in the execution of independent movements of the limbs, especially of their distal parts [768].

The motoneurons which belong to the medial motor system (Fig. 175B) innervate proximal muscles. They include the medial motor column of the anterior horn, which innervates the axial muscles and the somatomotor nuclei of the Vth, the dorsal (periorbital) part of the VIIth and the XIIth cranial nerves, which subserve bilateral movements. Interneurons belonging to the medial system

1 Motor cortex (area 4)
2 Premotor cortex (area 6)
3 Frontal eye field (area 8)
4 Tractus corticobulbaris et corticospinalis
5 Nucleus ruber
6 Fibrae hypothalamofugales et amygdalofugales
7 Colliculus superior
8 Griseum centrale mesencephali
9 Locus coeruleus
10 Tractus tectospinalis
11 Tractus rubrospinalis
12 Nucleus motorius nervi trigemini
13 Formatio reticularis lateralis
14 Formatio reticularis medialis pontis
15 Formatio reticularis medialis bulbaris
16 Tractus reticulospinalis
17 Nuclei vestibulares
18 Nucleus vestibularis lateralis
19 Tractus vestibulospinalis medialis
20 Tractus vestibulospinalis lateralis
21 Nucleus raphes pallidus
22 Nucleus nervi facialis, pars dorsalis
23 Nucleus nervi facialis, pars ventralis
24 Nucleus ambiguus
25 Nucleus nervi facialis
26 Decussatio pyramidum
27 Tractus pyramidalis lateralis
28 Tractus pyramidalis anterior
29 Substantia intermedia, pars dorsolateralis
30 Substantia intermedia, pars ventromedialis
31 Cellulae motoriae mediales
32 Cellulae motoriae laterales
33 Fasciculus longitudinalis medialis
34 Tractus raphespinalis
35 Tractus coeruleospinalis

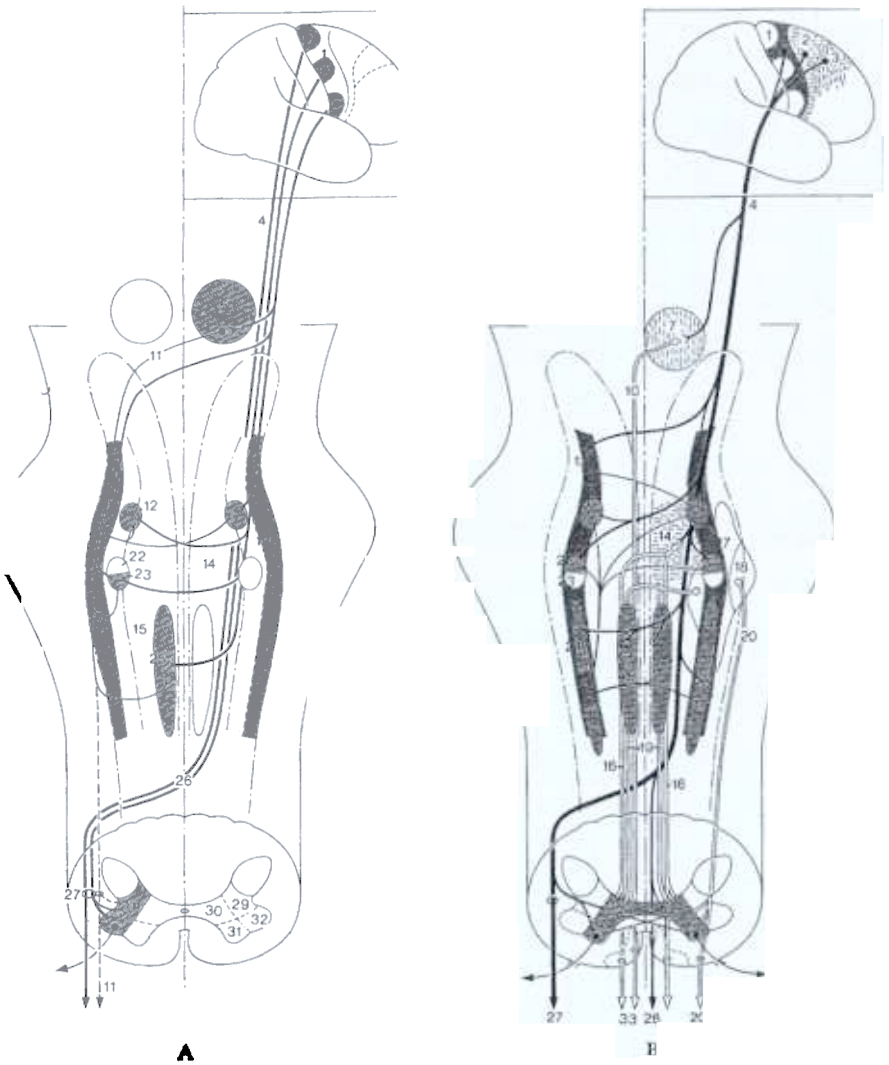


Fig. 175A–C. The neuronal connections of the lateral motor system (A), the medial motor system (B) and the motoneuronal connections of the locus coeruleus, the raphe nuclei and the medial reticular formation (C)

have long axons and often distribute bilaterally. In the cord they are located in the ventromedial part of the intermediate zone and in the brain stem they occupy the medial part of the lateral reticular formation. They project bilaterally to medially located anterior horn cells and to the nuclei of the XIIth, VIIth and Vth cranial nerves [538, 541, 545].

Several descending brain stem pathways, which terminate on these interneurons, belong to the medial motor system. All of these pathways descend in or near the medial longitudinal fascicle and the ventral funiculus of the cord. The medial reticulospinal tract [163, 193, 539, 1015] arises from the medial reticular formation of the pons. It descends bilaterally in the medial longitudinal fascicle and the ipsilateral ventral funiculus of the cord to terminate in the medial part of the intermediate zone. The medial and lateral vestibulospinal tracts also distribute their fibres to the medial part of the intermediate zone [163, 193, 744, 1015]. The medial vestibulospinal tract takes its origin from the medial vestibular nucleus and descends bilaterally in the medial longitudinal fascicle to terminate in the cervical cord. The lateral vestibulospinal tract, which arises from Deiters' nucleus, is an uncrossed pathway which descends lateral to the medial longitudinal fascicle and in the borderzone of the ventral and the lateral funiculus. It terminates throughout the cord and displays a prominent somatotopical organization. Both vestibulospinal tracts contribute fibres to the medial motoneuronal cell groups. The uncrossed interstitiospinal tract and the crossed tectospinal tract also terminate on medially located interneurons of the intermediate zone. Interstitiospinal fibres also establish synaptic contacts with neck motoneurons, whereas tectospinal fibres do not [193, 744, 1015]. The lateral vestibulospinal tract is an excitatory pathway for ipsilateral extensor motoneurons [1085]. The functional properties of the pontine reticulospinal pathway are incompletely known. Transsection of the medial systems at the level of the brain stem results in defects in the steering of integrated limb and body movements. Animals with combined lesions of the pyramidal tracts and the medial longitudinal fascicle failed to right and were unable to stabilize their arm in fine movements of the hand and the fingers, which they were able to execute normally [768].

Reticulospinal, Raphespinal and Coeruleospinal Systems

Until recently the medial reticulospinal fibres from the medulla oblongata and the pons were considered to belong to a single system with its main termination in the medial part of the intermediate zone [162, 1015]. It was shown, however, that fibres from the medial reticular formation of the medulla oblongata below the level of the facial nerve nucleus distribute more widely, far beyond the limits of the medial motor system, to the entire intermediate zone and the medial and lateral motoneuronal cell groups of the anterior horn throughout the spinal cord (Fig. 175C). They share this distribution pattern with the raphe spinal fibres from the nucleus raphe pallidus, many of which are serotoninergic, and with the fibres from the locus coeruleus and the nucleus subcoeruleus, many of which contain noradrenalin as a neurotransmitter [539, 745, 997]. The somatotopical organization of the reticulospinal tracts in their projection to the intermediate zone of the spinal cord is limited and much less pronounced than in the rubrospinal and lateral vestibulospinal tracts. In this respect they resemble the raphe-spinal projections [576]. The raphespinal and coeruleo-spinal pathways, which seem to exert a facilitatory action on motoneurons, and the medial bulbar reticulospinal system, which probably contains both inhibitory and excitatory components, therefore can be considered as parts of a third motor system, distinct from the medial and lateral systems considered before. The cerebral cortex, the cerebellum and the mesencephalic reticular formation, with their extensive projections to the medial bulbar reticular formation, may use this system to influence muscle tone. Moreover the third motor system provides to limbic system with an access to somatomotor control, through the connections of the hypothalamus, the amygdala and the central grey with the raphe nuclei and the locus coeruleus [543].

Direct and Indirect Cortico-motoneuronal Connections

The cortex projects to the entire pontine and bulbar reticular formation, the Vth, VIIth and XIIth cranial nerve nuclei, the intermediate zone and the anterior horn of the spinal cord. These projections are bilateral to the lateral reticular formation, the Vth and XIIth cranial nerve nuclei and the ventromedial parts of the intermediate zone and the anterior horn. The projections to the facial nerve nucleus, the dorsolateral part of the intermediate zone and the lateral motoneuronal groups of the anterior horn are predominantly crossed [738, 1220].

The direct projections to motoneurons innervating distal muscles of the limbs and the facial muscles take their origin from the caudal part of the motor cortex in the precentral gyrus (area 4, [176]). This is in accordance with the somatotopical localization in this area [1526]. Movements of the hindlimb, the forelimb and the face are localized in successively more lateral and ventral parts of the precentral gyrus. Both limb areas display a concentric arrangement, with movements around distal joints represented centrally and caudally, and movements around more proximal joints located in the intermediate and rostral parts of the motor cortex. Indirect projections to the lateral motor system, through the magnocellular part of the red nucleus and the crossed rubrospinal and rubrobulbar fibres arise from the same part of the motor cortex [223, 479, 831, 1076]. They display the same somatotopical organization in their origin and the focussing of their termination on the appropriate interneuronal and motoneuronal cell groups as the corticofugal pathway from the caudal motor cortex [52, 399, 533, 539, 544, 576, 1135, 1239, 1240].

The termination of the rubrobulbar and rubrospinal tracts includes the contralateral ventral periorbital part of the facial nerve nucleus, the lateral reticular formation and the spinal dorsolateral intermediate zone. At all these levels it completely overlaps the projection from the motor cortex. The size of the rubrospinal tract seems to be reduced in man [404, 1440]. It is questionable whether it continues beyond its rubrobulbar trajectory.

The direct projections of the cortex to the medial motoneuronal cell groups of the spinal cord and their interneurons in the medial part of the intermediate zone overlap the indirect projections of the cortex through the superior colliculus and the medial pontine reticular formation. Both the tectospinal tract and the medial reticulospinal tract terminate on the ventromedial intermediate zone of the spinal cord [539, 571]. The direct corticomotoneuronal connections and the projections from the cortex to the ventromedial intermediate zone are bilaterally organized and take their origin from a more rostrally located part of the motor cortex than the projections to the lateral motor system [744, 747]. The medial reticular formation receives its cortical input from the caudal part of the premotor area (caudal area 6) and the connections to the superior colliculus include still more rostral parts of the frontal lobe (areas 6 and 8 – the frontal eye field – and the adjoining prefrontal cortex) and parts of the parietal, occipital and temporal cortices [114, 363, 671, 672). The connections of area 6 with the spinal motor apparatus which passes through the medial bulbar reticular formation are not limited to the medial motoneuronal cell groups and the ventromedial part of the intermediate zone but involve the widespread projections of the reticulospinal component of the third motor system to the entire intermediate zone and the medial and lateral motoneuronal cell groups.

The eye muscle nuclei do not receive fibres from the cortex. Cortical control of eye

movements is achieved through the saccade generating centres in the mesencephalic tegmentum (rostral interstitial nucleus of the medial longitudinal fascicle [196]) and part of the medial (paramedian) pontine reticular formation [194], Cajal's interstitial nucleus of the medial longitudinal fascicle and the superior colliculus. The origins of the cortical projections to the saccade generating centres from the frontal eye field [778] overlap those to the projections to the superior colliculus.

It has been found that many of the fibres terminating in the basal pontine nuclei are collaterals of some of the fibre systems mentioned in this section. This holds for the massive projections to the central part of the pontine nuclei from the motor and sensory cortices, which take origin as a collateral projection of the pyramidal tract [1397] and for the projections to more peripheral parts of the pontine nuclei through the medial and lateral corticopontine divisions of the cerebral peduncle, which in part at least arise as collaterals from the corticotectal projection [15, 16, 68, 672].

The Pyramidal Tract Syndrome

The pyramidal tract syndrome in man results from an interruption of this tract's fibres anywhere along their long trajectory from the cortex to the motoneurons. It consists of a paralysis of voluntary muscle activity, enhanced tendon reflexes and muscle tone, disappearence of abdominal reflexes and the cremasteric reflex and inversion of the plantar response of the great toe (Babinski's sign). The extent and the laterality of the paralysis depend on the level of the lesion. In most cases other, indirect connections of the cortex with motoneurons are interrupted together with fibres of the pyramidal tract. The most frequent cause of a pyramidal syndrome is a lesion of the internal capsule, where the cortico-rubral, -tectal and -reticular fibres lie intermingled with fibres terminating on motoneurons and interneurons. The effects of isolated lesions of the pyramidal tract at the ventral aspect of the medulla oblongata are difficult to evaluate because in humans these cases are extremely rare [164]. Section of the pyramidal tract in monkeys results in a permanent loss of the ability to execute individual finger movements, but is not accompanied by hypertonia or increased tendon reflexes. The ability to fractionate movements remains the single, most important contribution of the pyramidal tract to motor control. It seems to be dependent upon the direct corticomotoneuronal connections which reach their highest development in man [164, 744, 767]. The hypertonia and the increase of the tendon reflexes of the pyramidal syndrome may be considered as release phenomena which appear when the shielding of the motoneurons from their reflex connections during voluntary, cortically induced movements is abolished and may be dependent on other, indirect pathways. Babinski's sign remains a reliable indicator of a lesion of the pyramidal tract. The dorsiflexion of the great toe and the spreading of the toes which occur on stimulating the sole of the foot when the pyramidal tract is interrupted should be considered as part of a flexion synergia, which is released when the pyramidal control of its interneurons is abolished and the direct cortical innervation of the motoneurons of the long extensor of the great toe is lost [1422].

The So-Called Extrapyramidal Motor System

Introduction

During the first decades of this century, the concept was developed that two independent systems, the pyramidal and the extrapyramidal, converge upon the spinal motor apparatus. In contrast to the direct corticospinal, pyramidal system, the extrapyramidal system was thought to be an array of centres which, together with their emergent fibres, constitute a multisynaptic descending system. Striopallidal, pallidorubral, rubrospinal and

reticulospinal pathways were considered to be the principal links in this system. Its highest centre, the striatum, was believed to receive its main input from the thalamus. Experimental hodological studies have shown that the idea of independently operating pyramidal and extrapyramidal systems has to be abandoned. The striatum and the other structures classically known as extrapyramidal centres are not interconnected in a unidirectional chain-like fashion. Rather, they and their emerging fibre systems constitute a number of interrelated loops or circuits, from which output systems emerge at several points. The following survey will first present the structure and positional relations of the various extrapyramidal centres and their fibre connections. This overview will be followed by some remarks about the internal organisation of the striatum. Then, the subdivision of the basal ganglia into dorsal and ventral districts, as has recently been proposed by several authors, will be considered and the most important connections of the so-called ventral striatum will be discussed. Finally, attention will be paid to the structure and connections of the basal nucleus of Meynert and some associated cell groups.

Structural Features

(see also Figs. 61–87; 88–109)

The striatum sensu stricto, i.e. the caudate nucleus plus the putamen, is by far the largest subcortical cell mass in the human brain. Its fresh volume is, according to Schröder et al. [1222], approximately 10 cm^3. Throughout its extent, the caudate nucleus is closely related to the telencephalic lateral ventricle (Fig. 28). Its large globular head rests on the anterior perforated substance and is anteriorly continuous with the putamen. The latter cell mass is situated medial to the insula and constitutes, with the pallidum or globus pallidus, the lentriform nucleus, a cone-shaped complex with the apex directed inwards. The putamen constitutes the outer part and the globus pallidus the inner part of the lentiform nucleus. The globus pallidus can be subdivided into an external and an internal segment. The anterior limb of the internal capsule largely separates the caudate nucleus from the putamen, whereas the posterior limb of the internal capsule occupies the space between the lentiform nucleus and the thalamus.

Structurally the caudate nucleus and the putamen are identical. They have a homogeneous structure throughout and contain numerous medium-sized neurons, among which conspicuous large cells are sparsely scattered. A quantitative analysis [1222] has revealed that in the human striatum sensu stricto about 100 million medium-sized and some 600000 large cells are present.

The globus pallidus, which is of diencephalic origin, differs considerably, histologically, from the telencephalically derived striatal nuclei. It is chiefly composed of rather large, widely spaced, fusiform cells. The total number of pallidal cells is, in humans, about the same as that of the large striatal neurons, i.e. 600000 [1372]. The globus pallidus is subdivided into a lateral or external and a medial or internal segment. In primates these two segments are demarcated from each other by the medial medullary lamina.

The nucleus accumbens is a cell mass which lies closely apposed to the most rostroventromedial part of the caudate-putamen complex. Structurally, this nucleus cannot be sharply delimited from the striatum.

The subthalamic nucleus is a conspicuous, large-celled nucleus that is situated in the most caudal part of the diencephalon, dorsomedial to the posterior limb of the internal capsule. Its medial part overlies the rostral portion of the substantia nigra.

The substantia nigra is the largest cell mass of the mesencephalon. Lying between the tegmentum and the cerebral peduncle, its most rostral part extends into the diencephalon and closely approaches the globus pallidus. The substantia nigra can be divided into a dorsal, cell-rich, pars compacta and a ventral, less cellular, pars reticulata. The pars compacta is composed of large polygonal

cells which synthesise dopamine. Many of the dendrites of these elements extend ventrolaterally into the pars reticulata. The cells in the pars reticulata are somewhat smaller than those in the pars compacta. It is noteworthy that the pars reticulata of the substantia nigra has many features in common with the internal segment of the globus pallidus. The dopaminergic neurons in the pars compacta are often designated cell-group A9 [279].

In addition to the pars compacta of the substantia nigra, there are two other mesencephalic nuclei, the cells of which synthesise dopamine. These cell groups, neither of which can be sharply delimited from the substantia nigra, are known as the ventral tegmental area of Tsai (A10) and the nucleus parabrachialis pigmentosus (A8). The former is situated in the rostromedial part of the mesencephalic tegmentum; the latter lies in the dorsolateral part of the same area and forms part of the reticular formation.

Another nucleus which is included in the circuitry of the basal ganglia is the nucleus tegmentalis pedunculopontinus, pars compacta. This rather small cell mass is situated in the caudal part of the tegmentum of the midbrain and lies also embedded into the reticular formation (Fig. 101).

Fibre Connections

In the ensuing survey of the connections of the striatum and related 'extrapyramidal' centres, we will distinguish a principal striatal circuit and four "accessory" striatal circuits. Following the discussion of these circuits attention will be focussed on some recent additions to our knowledge of the 'extrapyramidal' circuitry and on its input and output channels. Because the fibre connections to be discussed are extensively documented in several review articles [442, 890, 996], references will be mainly confined to the most recent literature. It should be emphasised that the description of the connections of the caudate nucleus does not hold for the nucleus accumbens. The fibre systems related to this and adjacent ventral striatal sectors will be treated separately below.

1. The Principal Striatal Circuit: Cerebral Cortex – Striatum – Globus Pallidus – Thalamus – Cerebral Cortex (Figs. 171, 173, 176, 177). Contrary to the views of previous workers it has been established that the whole of the neocortex sends fibres to both the caudate nucleus and the putamen and that all parts of these two cell masses receive fibres from the cortex. It was originally held that the arrangement of this corticostriate projection is on a simple topographical basis in that particular cortical areas project to proximal portions of the striatum [210, 676]. However, more recent studies [413, 733, 734, 1227, 1431, 1543] have shown that the terminal fields of the corticostriate fibres originating from circumscribed cortical regions are arranged in narrow, longitudinally arranged strips or bands, which often span the entire length of the nucleus. Most cortical areas project only to the ipsilateral striatum, but the premotor (6, 8), motor (4) and somatosensory (3, 1, 2) cortical areas have been shown to be distributed bilaterally [633, 676, 733, 734]. The fibres arising from the motor cortex project in a somatotopic fashion upon the putamen (dorsal to ventral: leg, arm, face) [733]. The corticostriate fibres, which are thought to have the excitatory aminoacid glutamate as their neurotransmitter [353], establish direct synaptic contacts with the principal striatal efferent neurons, i.e. the so-called medium-sized spiny cells [1270]. These highly characteristic cells are very common in the striatum.

Efferent fibres from the striatum converge towards the globus pallidus, where they constitute a massive fibre system, which passes radially through both pallidal segments. During their transit through the globus pallidus the fibres of this system emit numerous collaterals that synapse with pallidal neurons. The striatofugal bundle then leaves the globus pallidus and descends to the substantia nigra, passes through the internal capsule, then terminates mainly in the pars reticulata

of that structure. It was previously believed that the striatal projections terminating in the external and internal segments of the globus pallidus are collateral branches of striatonigral fibres [357, 358], but studies using double retrograde tracing [93, 1018] have shown that these three projections come mainly from separate cell populations. In striatofugal projection neurons several neuroactive principles, among which are GABA, substance P, enkephalin and dynorphin, have been shown to be present [438, 443, 997]. Although there is evidence suggesting that GABA and enkephalin coexist in many striatal cells, it has been shown that substance P is present only in striatal neurons that do not contain GABA or enkephalin [93]. Given the facts that: (a) the external segment of the globus pallidus is particularly densely innervated by enkephalinergic striatofugal fibres, but contains only sparse substance P- and dynorphin-immunoreactive axones; (b) the internal segment of the globus pallidus and the substantia nigra, pars reticulata contain dense networks of substance P- and dynorphin-positive striatal axons, but few that are reactive for enkephalin; and (c) GABA-ergic striatofugal fibres are numerous in all three target structures, but form a particularly dense plexus in the substantia nigra [93, 438, 443, 997], it may be concluded that the external segment of the globus pallidus on the one hand, and the internal segment of the globus pallidus and the substantia nigra on the other hand are at least in part preferentially innervated by different sets of chemically specified striatofugal neurons [93].

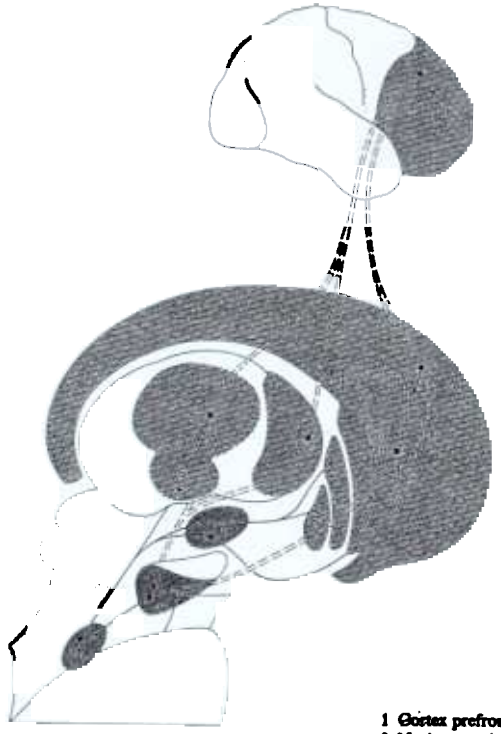
The quantitatively most important efferent system of the striopallidum is the pallidothalamic projection. This projection originates exclusively from the medial pallidal segment. Its fibres, which are thought to contain GABA, initially constitute two separate bundles, the fasciculus lenticularis and the ansa lenticularis. The fibres merge in Forel's field H, after which they ascend as a single bundle, the fasciculus thalamicus, to the rostral part of the thalamus [988]. The fibres of this pallidothalamic projection, which is topographically organised [297, 687, 737], terminate in the rostral part of the ventral lateral nucleus of the thalamus [1365]. This portion of the ventral lateral thalamic nucleus is known to project to part of cortical area 6, including the supplementory motor area [1215, 1302, 1365). The neurotransmitter present in this thalamocortical projection is not known.

The existence of the projections just described, which are all topically organised, strongly suggests that information derived from the entire neocortex is processed in the striatum, the globus pallidus and the thalamus, respectively, and then is fed back into the premotor and supplementory motor areas of the cerebral cortex.

2a. The First 'Accessory' Striatal Circuit: Striatum – Globus Pallidus – Thalamus – Striatum. The striopallidal and pallidal efferent fibres, which form the initial part of this circuit, have already been dealt with. It has been shown that a considerable number of fine, presumably collateral fibres leave the fasciculus thalamicus before it reaches the ventral lateral nucleus. These fibres enter the internal medullary lamina and terminate in the centromedian and parafascicular nuclei [297, 687, 737, 988]. As has already been mentioned (cf. Section Ascending Reticular System) fibres arising from these intralaminar nuclei project massively upon the striatum [885]. There is a clear differential distribution of the striatal fibres originating from the centromedian/parafascicular complex, the centromedian nucleus projecting exclusively to the putamen and the parafascicular nucleus only to the caudate nucleus [1264]. The centromedian and parafascicular nuclei do not project only to the striatum, but also to the cerebral cortex. It has been established that these two projections arise in separate neurons [1293]. The thalamostriate fibres terminate, like the corticostriate axons, upon medium-sized spiny neurons [678] and are thought to be excitatory [337]. The neurotransmitter utilised by the thalamostriate fibres is not known.

1 Premotor cortex (area 6)
2 Nucleus caudatus
3 Putamen
4 Nucleus parafascicularis + nucleus centromedianus
5 Nucleus ventralis lateralis thalami
6 Globus pallidus, pars lateralis
7 Globus pallidus, pars medialis
8 Nucleus subthalamicus
9 Substantia nigra, pars compacta
10 Substantia nigra, pars reticulata

Fig. 176. The principal striatal circuit and the first, second and third "accessory" striatal circuits, indicated by framed numbers, as described in the text. Bold lines: principal circuit



1 Cortex prefrontalis
2 Nucleus caudatus
3 Putamen
4 Nucleus ventralis anterior thalami
5 Nucleus medialis thalami
6 Nuclei intralaminares thalami
7 Globus pallidus, pars lateralis
8 Globus pallidus, pars medialis
9 Nucleus subthalamicus
10 Substantia nigra, pars reticulata
11 Nucleus tegmentalis pedunculopontinus, pars compacta

Fig. 177. The fourth "accessory" striatal circuit and some ascending connections of the subthalamic nucleus, the substantia nigra, pars reticulata and the nucleus tegmentalis pedunculopontinus, pars compacta

Physiological evidence indicates that by way of the thalamostriatal projection polysensory information is fed into the striatum. Krauthamer [714] has expressed the opinion that this information may be important inter alia for the execution of appropriate orienting responses. He proposes that the loop between the intralaminar nuclei and the striatum enables the latter structure to self-regulate its polysensory input.

2b. The Second 'Accessory' Striatal Circuit: Globus Pallidus – Corpus Subthalamicum – Globus Pallidus. The lateral part of the globus pallidus projects in a topically organised fashion on the subthalamic nucleus [214, 217, 872, 988] and the latter centre is known to project massively back to all parts of the globus pallidus [214, 215, 973, 974]. GABA has been suggested as the probable neurotransmitter in both the pallidosubthalamic and the subthalamopallidal projection [352, 975, 1160]. Physiological experiments have shown that the predominant response of globus pallidus neurons to stimulation of the subthalamic nucleus is inhibition [1068]. Clinicopathological and experimental evidence indicate that lesions of the subthalamic nucleus lead to contralateral hemiballism, a vigorous involuntary hyperkinesia of the extremities with a repetitive, stereotyped character [471, 1505]. Most probably interruption of the inhibitory, GABA-ergic subthalamopallidal fibres is a salient feature in the neural mechanism of this subthalamic hyperkinesia [268].

2c. The Third 'Accessory' Striatal Circuit: Striatum – Substantia Nigra – Striatum. It has already been mentioned that fibres originating from the caudate nucleus and the putamen traverse the globus pallidus and subsequently descend to the substantia nigra. This strongly developed projection is topically organised [455, 1345]. Its fibres terminate mainly, but not exclusively, in the external, reticular part of the substantia nigra. The striatonigral connection contains large numbers of GABA-, substance P- and dynorphin-positive fibres, all of which form dense networks in the substantia nigra. A more restricted contingent of enkephalinergic fibres is also present in the striatonigral projection [438, 443, 997].

The major ascending efferent projection of the substantia nigra is formed by a system of extremely fine axons, which originates from the dopaminergic cells in the pars compacta of that structure [30, 279, 1363, 1402]. This projection is topically organised in three planes, medial-lateral, rostral-caudal and dorsal-ventral [220, 337]. The nigrostriatal dopaminergic neurons establish direct synaptic contacts with striatonigral projection neurons [361], but pharmacological evidence suggests that these fibres exert an additional presynaptic action on the glutamatergic corticostriate fibres [705].

There is evidence that the dopaminergic nigrostriatal projection participates in the regulation of complex behaviour and plays a crucial role in determining the ability of the organism to cope with available exteroceptive sensory information in various ways. This specific capacity has been denoted as "the ability to arbitrarily switch motor programmes" [256, 257, 614].

Parkinson's disease is characterised by a progressive loss of dopaminergic neurons in the pars compacta of the substantia nigra, with consequent degeneration of their ascending projections and reduction of the dopamine content in the striatum. In relation to what has been stated above concerning the functions in which the nigrostriatal projection is involved, it is worthy of note that patients suffering from Parkinson's disease appear to have an impaired ability to switch their behaviour [258].

Striatonigral fibres synapse directly with nigrostriatal neurons [1271, 1478], and there is evidence indicating that the striatum and the substantia nigra are interconnected in point-to-point reciprocity [1264]. Moreover, it has been shown that striatal substance-P-containing neurons which project selectively to the internal segment of the globus pallidus and the substantia nigra are a preferential target for nigrostriatal dopaminergic innervation [92]. It is, however, not the case that the entire striatonigral projection represents only a 'returnloop' modulating the reciprocating nigrostriatal system. The fibres of the striatonigral system also synapse on the non-dopaminergic neurons of the pars reticulata, elements which, as will be discussed below, form part of another 'accessory striatal circuit' and also contribute substantially to the output system of the corpus striatum.

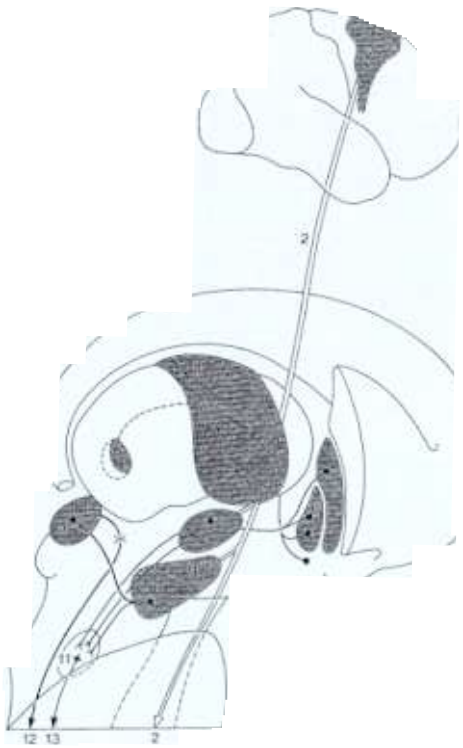
2d. The Fourth 'Accessory' Striatal Circuit: Cortex – Striatum – Substantia Nigra – Thalamus – Cortex (Fig. 177). A substantial nigrothalamic projection originates from the reticular part of the substantia nigra. Its fibres are distributed over certain parts of the ventral anterior and medial thalamic nuclei [219, 586], which project to large areas of the dorsolateral and orbitofrontal association cortex, the frontal eye field, and the supplementory motor area [586].

3. Recently Established Additional Pathways. With the aid of the modern anterograde and retrograde tracer techniques a considerable number of additional "extrapyramidal" fibre connections has been established, only a few of which will be mentioned here. It has been shown that the nucleus subthalamicus not only sends numerous fibres to the globus pallidus, but also projects to the caudate nucleus and the putamen [90], to the pars reticulata of the substantia nigra [215, 872, 974, 1121] and to the nucleus tegmentalis pedunculopontinus, pars compacta (TPC) [319, 601]. The latter cell mass, which until recently was only known to receive a projection from the globus pallidus [988], also takes up fibres from the pars reticulata of the substantia nigra [94, 95, 319, 1053]. The neurons constituting the latter projection utilise GABA as their neurotransmitter [237]. The TPC has been shown to give rise to a small descending and a much larger ascending efferent projection. The former will be considered below; the latter is distributed mainly to the globus pallidus, the intralaminar nuclei of the thalamus and the subthalamic nucleus [319, 602, 890, 1002, 1192, 1312]. The large neurons constituting the TPC are thought to be cholinergic [963, 1312]. It will be clear that the connections just mentioned close a considerable number of additional "extrapyramidal" loop systems.

4. Input systems (Fig. 177). The reticular formation of the brain stem has a quantitatively very important access to the "extrapyramidal" circuitry. The reticular formation, particularly its mesencephalic portion, is one of the principal sources of afferent fibres to the intralaminar nuclei of the thalamus and, as pointed out earlier, the latter projects to both the caudate nucleus and the putamen. A second important input system to be mentioned here is the mesostriatal serotoninergic projection, which originates mainly from the dorsal raphe nucleus and terminates throughout the striatum, but more, significantly in its ventral and medial regions [31, 134, 397, 951, 1264, 1346, 1347].

Before leaving the input systems it should be mentioned that our knowledge of the afferent connections of one important extrapyramidal centre, the pars compacta of the substantia nigra, is remarkably scant. Striatonigral fibres terminate mainly on the dendrites of the compacta cells which extend into the pars reticulata. Several other sources of afferents to the pars compacta have been suggested, among which are the globus pallidus, the central amygdaloid nucleus, the lateral hypothalamic area and the habenula, but none of these connections has been established unequivocally [890]. An afferent projection to the pars compacta arising from the TPC, which has been described by several authors [319, 449, 1002, 1192], could not be confirmed by ultrastructural analysis [1312].

5. Output Channels (Fig. 178). Because the main outflow from the striatum and the nuclei related to it converges, via the globus pallidus and the thalamus upon the premotor cortex, the fibres originating from this cortical area constitute the principal output channel of all of these nuclei. Prominent among



1 Premotor cortex (area 6)
2 Tractus pyramidalis
3 Nucleus ventralis lateralis thalami
4 Nucleus habenulae lateralis
5 Globus pallidus, pars lateralis
6 Globus pallidus, pars medialis
7 Nucleus subthalamicus
8 Colliculus superior
9 Substantia nigra, pars compacta
10 Substantia nigra, pars reticulata
11 Nucleus tegmentalis pedunculopontinus, pars compacta
12 Fasciculus predorsalis (tractus tectobulbospinalis)
13 Fibrae pedunculopontino-reticulares

Fig. 178. Output channels of the so-called extrapyramidal motor system

the systems emanating from this cortical area is, of course, the motor part of the pyramidal tract, but this area also gives rise to a number of other projections, some of which may well consist of collaterals of the pyramidal axons. Such projections terminate in the ventral lateral nucleus of the thalamus [742, 890], the subthalamic nucleus [478, 1076], the substantia nigra pars compacta [1405], the TPC [319] and in the reticular formation of the brain stem. Several of these pathways feed back into centres included in one of the striatal circuits, thus closing additional "accessory" loops. The remaining output pathways of the extrapyramidal motor system include pallidohabenular, nigrotectal, nigrotegmental and pedunculopontinoreticular projections.

The pallidohabenular fibres originate from the medial pallidal segment and terminate in the lateral habenular nucleus [297, 509, 971]. In primates this projection originates from a peripheral zone of the medial pallidal segment, which encroaches upon the lateral hypothalamus [1052, 1053]. Nauta and Domesick [985] have pointed out that the lateral habenular nucleus projects directly to the mesencephalic raphe nuclei and is probably a principal source of afferents to the serotoninergic cells contained within these nuclei. They conjectured that the pallidohabenular connection could form part of a neural circuit: pallidum – lateral habenular nucleus – dorsal raphe nucleus – striatum – pallidum.

The nigrotectal and nigroreticular projections originate both from the pars reticulata of the substantia nigra [95, 435, 445, 551, 1129]; both are thought to be inhibitory and to utilise GABA as their neurotransmitter [233, 237]. The massive nigrotectal projection terminates in a highly regular bandpattern in the middle grey layer of the superior colliculus. The same layer contains the cells from which the predorsal fascicle arises [868]. This is a large descending bundle which distributes fibres to a considerable number of premotor and motor centres in the brain stem and spinal cord (cf. The section Visual System). The nigrotegmental fibres terminate mainly in the TPC, but some descend to the medullary reticular formation. The TPC, which is situated in the caudolateral midbrain tegmentum, roughly corresponds to an area known as the mesencephalic locomotor region. This centre receives, apart from a projection from the substantia nigra pars reticulata, afferents from the motor cortex [748], the globus pallidus [214, 297, 687, 988, 1339] and the subthalamic nucleus [319, 601, 974]. Its efferents include ascending fibres which terminate in the subthalamic nucleus, intralaminar nuclei of the thalamus and the globus pallidus, and descending fibres which constitute a pedunculopontinoreticular projection. The latter has been observed to terminate in the pontine and medullary parts of the medial reticular formation [319, 381, 382, 602].

In summary, according to our present state of knowledge, the striatum has four parallel conduction lines along which the motor centres in the brain stem and spinal cord may be influenced. These pass: (1) Via the globus pallidus and the thalamus to the premotor cortex and the pyramidal tract; (2) From the striatum, via the substantia nigra pars reticulata, to the superior colliculus; (3) Directly from the substantia nigra to the reticular formation; (4) From the globus pallidus and the substantia nigra pars reticulata, to converge upon the TPC, accompanied by descending efferents from the TPC.

Aspects of the Organisation of the Striatum

The so-called medium-sized spiny cells, which are present in enormous numbers in the caudate nucleus and the putamen, occupy a central position in the circuitry of those centres. The name of these neurons refers to the fact that their dendrites, which radiate and ramify in all directions, are densely covered with spines [154, 303, 433, 677]. The principal afferent systems to the striatum are: glutamatergic fibres from the cerebral cortex [353, 678, 1270], fibres originating from the intralaminar thalamic nuclei (whose neuro-

transmitter is still unknown) [678], dopaminergic fibres from the substantia nigra [725] and serotonergic fibres from the dorsal raphe nucleus [1057]. All synapse with the medium-size spiny cells. The medium-sized spiny cells have long axons which leave the striatum. These axons, which terminate in the globus pallidus and the substantia nigra, constitute the principal efferent system of the striatum. Medium-sized spiny cells contain GABA [349, 1018], substance-P [140], enkephalin [302] or dynorphin [1447], and frequently GABA as well as enkephalin [57].

In addition to the extrinsic afferents discussed above, several groups of intrinsic elements impinge upon the medium-sized spiny cells. Under this heading the medium-sized spiny cells themselves should be mentioned first because, apart from their long projection axons, these elements give off numerous local collateral branches within the striatum, which have been shown to contact other neurons of the same type. Other local-circuit neurons synapsing with medium-sized spiny cells include large elements with aspiny dendrites, containing acetylcholine, GABA-ergic medium-sized aspiny cells and neurons of the same type containing somatostatin. In addition, intrinsically organised medium-sized aspiny neurons containing VIP [696], CCK [1352] and neuropeptide Y [1263, 1265] have been found. The place of these elements in the striatal microcircuit remains to be determined.

Huntington's disease is a rare, dominantly inherited neurodegenerative disorder, characterised by involuntary choreatic movements and progressive dementia. The most striking neuropathological feature of this disease is severe atrophy of the striatum, with marked neuronal loss and gliosis. It is worthy of note that the medium-sized aspiny cells containing somatostatin are the only class of neuron in the striatum to escape degeneration during the progression of the disease [345].

Cytoarchitectonically the caudate-putamen complex is a homogeneous structure, but histochemical and particularly immunohistochemical studies have revealed a remarkable heterogeneity within the complex. The first evidence for this chemoarchitectural heterogeneity came from studies in which a staining technique for the enzyme acetylcholinesterase (AChE) was applied. These studies showed that in the caudate-putamen complex, 300- to 600-μm-wide zones of low AChE activity stand out against an otherwise AChE-rich background. Graybiel and Ragsdale [441, 442], who first identified these zones, designated them striatal bodies or *striosomes*. Graphical reconstructions have shown that in most places the striosomes form part of a complex three-dimensional labyrinth. During recent years it has gradually become clear that throughout most of the caudate-putamen complex the striosomes and the "matrix" in which they are embedded represent chemoarchitectonically distinct tissue compartments, which are related to the intrinsic structure of the complex as well as to the organisation of its afferent and efferent connections. The following features may be mentioned in this context (for details cf. the review articles of Graybiel [437, 438]; and Graybiel and Ragsdale [441, 443]):

1. Apart from a low AChE concentration, the striosomes show high enkephalin, substance-P, GABA and neurotensin immunoreactivity [390, 444].

2. The complementary matrix compartment shows, in addition to a high AChE concentration, a dense plexus of somatostatin-containing fibres [390].

3. The striosomes show a remarkably high concentration of opiate receptors [1072].

4. Neurons expressing high levels of immunoreactivity to substance P are clustered along with dynorphin-positive neurons in the striosomes. By contrast enkephalin-positive neurons, somatostatin-positive neurons and the large cholinergic interneurons tend to lie outside these zones [437, 438].

5. The striosomes appear to coincide with patches of high dopamine density, the so-called "dopamine islands", which correspond to a distinct, early-developing contingent of nigrostriatal fibres [436, 443].

6. Studies with anterograde tracers have revealed that not only the nigrostriatal pathway, but also the thalamostriatal and corticostriatal projections, terminate in a patchy fashion. It has been demonstrated that the terminal patches of the thalamostriatal fibres avoid the striosomes [437, 511]. The massive corticostriatal projection can be divided into two fibre contingents, one that avoids the striosomes and another that projects specifically to them. Thus, the motor, somatosensory and visual areas preferentially project to the matrix compartment, but the efferents from the prelimbic cortex are distributed to the striosomes [311, 390].

7. There is some evidence indicating that the striatal projection neurons are also differentially distributed over the two striatal compartments. Following injections of a retrograde tracer in the internal pallidal segment or in the substantia nigra pars reticulata, labelled neurons appear to be most densely distributed in the matrix compartment, whereas after injections centred in the compact part of the substantia nigra, labelled neurons are located preferentially in the striosomes [390, 391, 438].

From the foregoing synopsis it may be concluded that the caudate-putamen complex displays an intriguing mosaic-like chemical heterogeneity and that several structural and connectional features fit into this mosaic.

Subdivision of the Basal Ganglia into Dorsal and Ventral Sectors

With regard to the extent of the striatum and the globus pallidus Heimer and his coworkers [493, 496, 497] have advanced a view, the essence of which may be summarised as follows: The caudate nucleus, putamen and globus pallidus, as usually delineated, represent only the dorsal part of the striatal complex. The nucleus accumbens, which cytoarchitectonically as well as histochemically closely resembles the caudate nucleus and putamen, and certain parts of the olfactory tubercle should be considered together as a ventral portion of the striatum. The rostral part of the substantia innominata, another basilar forebrain structure, represents a ventral extension of the globus pallidus. The ventral striatum and the ventral pallidum are nodal points in a loop system which forms a striking pendant of the principal striatal circuit, described above. This loop includes: (1) the allocortex, (2) the nucleus accumbens, i.e. the ventral striatum, (3) the ventral pallidum, (4) the medial thalamic nucleus, (5) the prefrontal, prelimbic and cingulate regions, (6) cortical area 6, which receives projections from certain parts of the cortical regions mentioned under (5). The well-known fact that the nucleus accumbens receives a strong dopaminergic input from the ventral tegmental area, whereas the caudate-putamen complex receives a similar projection from the substantia nigra, further substantiates the interpretation of the nucleus accumbens as a ventral striatum.

Given the fact that the allocortex forms part of the limbic system Heimer et al. [496] conjecture that, whereas the dorsal striatopallidal system plays a pre-eminent role in initiating motor activities stemming from cognitive activities, the ventral striatopallidum has a role in initiating movements in response to emotionally or motivationally powerful stimuli.

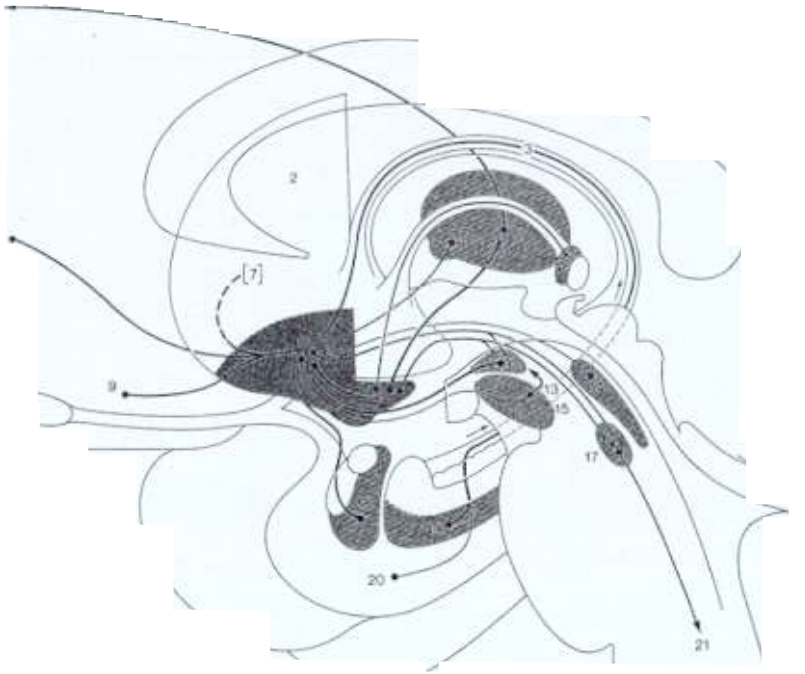
A concept related to that of Heimer and his associates has been recently put forward by Kelly, Domesick and Nauta [675]. These authors found that in the rat a voluminous amygdalostriatal projection is present, which is distributed to all parts of the striatum except the antero-dorso-lateral quadrant. They pointed out that this projection widely overlaps the striatal projections from the hippocampus, the cingulate cortex, the ventral tegmental area and the mesencephalic raphe nuclei. Like the amygdalostriatal system, all of these striatal afferents avoid the antero-dorso-lateral striatal sector. Kelley et al. [675] further established that the striatal sector just mentioned is the main region to which the corticostriatal projection is distributed from

the sensorimotor cortex. In view of these findings they interpreted the large striatal region receiving a direct projection from the amygdala as the "limbic" and the remainder as the "non-limbic" striatal compartment. Kelley et al. [675] suggested that the amygdala, which is known to play a role in the neural mechanisms underlying motivation and adaptive behaviour, has access via its massive projection to the striatum, to the initiation and patterning of somatomotor behaviour in which the latter structure is involved. It is important to note that the nucleus accumbens is included in the "ventral" striatum as well as in the "limbic" striatum, but that the former entity extends further dorsally than the latter.

Fibre Connections of the Ventral Striatum (Figs. 179–181)

The nucleus accumbens and adjacent sectors of the caudate nucleus and the putamen receive afferents from the cerebral cortex, particularly from its limbic areas, the amygdala, the midline nuclear complex of the thalamus, the ventral tegmental area and the dorsal raphe nucleus [208, 448, 449, 993]. The cortical afferents originate from the medial frontal cortex, the prelimbic cortex, the posterior part of the insular cortex, the perirhinal and entorhinal cortices and the hippocampal subiculum. There is a topographical relationship between the subiculum and the nucleus accumbens: the rostral (uncal) part of the hippocampus projects to the medial nucleus accumbens, whereas the caudal (splenial) part of the hippocampus is connected with more rostral and lateral parts of this nucleus [449]. The cortical neurons projecting to the ventral striatum are thought to be excitatory and to utilise either glutamate or aspartate as their neurotransmitter. The amygdalostriatal projection arises mainly from the basal amygdaloid nuclei. Just like the hippocampal efferents, the amygdalostriatal projection is topographically organised [1170, 1171, 1273]. The ventral tegmental area projects to the entire ventromedial half of the striatum, but most massively to the ventral striatal zone that includes the nucleus accumbens [94, 1346, 1347]. The dopaminergic innervation of the ventral striatum, which originates mainly from the ventral tegmental area, is very strong and unevenly distributed. This uneven distribution of dopaminergic terminals is paralleled by the uneven distribution of the neuropeptides enkephalin, substance P and dynorphin and the neurotransmitter GABA [1463]. It is noteworthy that many neurons in the ventral tegmental area which project to the ventral striatum contain cholecystokinin [1410, 1547] and that in some of these elements cholecystokinin is co-localised with dopamine [529, 532].

The efferents of the ventral striatum pass primarily to extrapyramidal centres, like the ventral pallidum, the ventral tegmental area and the pars compacta and pars reticulata of the substantia nigra, but a number of limbic-related structures, such as the septum, the bed nucleus of the stria terminalis, the medial hypothalamus, the central superior nucleus and the periaqueductal grey matter are also innervated [450, 989, 993]. The projection from the nucleus accumbens to the ventral pallidum contains a major GABA-ergic component [930], and substance-P-, enkephalin- and dynorphin-positive fibres have also been shown to be present within this projection [462, 463]. The enkephalin- and substance-P-positive fibres constitute dense and highly characteristic terminal plexuses within the ventral pallidum. The plexus of enkephalinergic fibres continues dorsally without interruption, into the main mass of the pallidum. In contrast, the plexus of substance P-positive fibres extends for only a very short distance into the main pallidal mass, and thus provides a criterion for determining the extent of the ventral pallidum [87, 461, 462]. It has been demonstrated that the accumbofugal efferents to the ventral pallidum project monosynaptically to output cells of that structure [1536]. A similar direct, monosynaptic relationship has been observed between the efferents of the accumbens nucleus which



1 Cortex prefrontalis
2 Striatum dorsale
3 Fornix
4 Nuclei mediani thalami
5 Nucleus medialis thalami
6 Nucleus habenulae lateralis
7 Cortex insulae
8 Cortex prelimbicus
9 Cortex prefrontalis medialis
10 Striatum ventrale
11 Pallidum ventrale
12 Area tegmentalis ventralis
13 Fibrae nigrostriatales
14 Nucleus raphes dorsalis
15 Substantia nigra, pars compacta
16 Substantia nigra, pars reticulata
17 Nucleus tegmentalis pedunculopontinus pars compacta
18 Nuclei basales amygdalae
19 Subiculum
20 Cortex entorhinalis + perirhinalis
21 Fibrae pedunculopontino-reticulares

Fig. 179. Principal connections of the ventral striatum and the ventral pallidum

pass to the pars compacta of the substantia nigra and nigrostriatal projection neurons [1271]. In the light of this observation, it is plausible that a strong limbic input from the hippocampus and the amygdala, via the accumbens nucleus and subsequently through the dopaminergic cells in the substantia nigra, may reach the main, dorsal mass of the striatum [450].

The ventral pallidum receives, in addition to a massive projection from the ventral striatum, afferents from: (1) the amygdaloid complex, particularly its basal nuclei, (2) several cortical areas, including the orbitofrontal cortex, the anterior insular cortex, the anteroventral part of the temporal lobe and the entorhinal and piriform areas, (3) the midline thalamic nuclear complex, (4) the hypothalamus, particularly the perimamillary region, and (5) several centres in the brain stem, including the ventral tegmental area, the pars compacta of the substantia nigra, the mesencephalic raphe nuclei, the parabrachial area and the reticular formation [1168]. It is, however, important to note that most of these five contingents of afferents have been traced to the substantia innominata and the magnocellular basal nucleus embedded therein (see below), rather than specifically to the restricted rostral part of the substantia innominata, which represents the ventral pallidum.

The efferents of the ventral pallidum are distributed to the basal nuclei of the amygdaloid complex, the lateral habenula, the medial thalamic nucleus, the ventral tegmental area and to more-caudal regions of the midbrain tegmentum, including the pars compacta of the pedunculopontine tegmental nucleus (TPC) [384, 461, 931, 932, 1338). The fibres passing to the medial thalamic nucleus are a link in a projection from the ventral striopallidum to the medial prefrontal cortex [496, 1449]. According to Nauta [984], it is likely that through this circuit the ventral striopallidum can affect the cognitive functions subserved by the medial prefrontal cortex. The conduction line leading from the accumbens nucleus via the ventral pallidum to the TPC and surrounding structures is paralleled by a direct projection from the nucleus accumbens to the same area [436, 450]. As has already been pointed out, the TPC corresponds roughly to the so-called mesencephalic locomotor region [381, 932, 1259, 1338]. Pharmacological and physiological evidence suggest that the accumbens nucleus constitutes an interface between the limbic and the motor system, subserving a gate function for goal-directed behaviours, particularly locomotion [929]. The subicular inputs appear to have direct access to ventral striatal output neurons, which in their turn project monosynaptically to the ventral pallidum. The majority of the ventral pallidal neurons are inhibited by subicular stimulation. This may be explained by the fact that an excitatory, presumably glutamatergic projection from the subiculum to the ventral striatum, activates GABA-ergic ventral striatal neurons which project to the ventral pallidum, where they exert an inhibitory influence [1536]. Mogenson and Nielsen [930] provided pharmacological evidence suggesting that the GABA-ergic projection from the accumbens nucleus to the ventral pallidum contributes to locomotor activity. It has also been shown that manipulation of the dopaminergic transmission in the nucleus accumbens influences locomotor behaviour [1090]. As mentioned, the TPC projects to the pontine and medullary reticular formation. Recently, some of the reticular elements receiving afferents from the TPC have been demonstrated to project to the spinal cord [383], thus completing a long, polysynaptic conduction line from the limbic system to the motor system.

In summary, the ventral striatum has three major output systems: one passing via the ventral pallidum and the medial thalamic nucleus to the prefrontal cortex; a second leading via the pars compacta of the substantia nigra and its dopaminergic efferents to the dorsal striatum; and a third by which the ventral striatum – via the ventral pallidum, the TPC and the reticular formation – has access to the somatomotor system.

The Magnocellular Basomedial Telencephalic Complex

The basal forebrain contains a population of large cholinergic neurons, extending from the septal region rostrally to the level of the subthalamic nucleus caudally. Mesulam and collaborators [904, 905, 907] subdivided this population in the monkey into four groups, Ch1-Ch4 (for a map of these cell masses in the human brain, see Perry et al. [1069], Hedreen et al. [488] and Saper and Chelimsky [1189]):

1. The Ch1 group is found in the medial septal nucleus; about 10% of the neurons in this centre are cholinergic.

2. The Ch2 group corresponds to the vertical limb of the nucleus of the diagonal band of Broca; at least 70% of its neurons are cholinergic.

3. The Ch3 group is embedded within the horizontal limb of the nucleus of the diagonal band of Broca; only 1% of the neurons in this nucleus are cholinergic.

4. The Ch4 group, which is very extensive in the human brain, corresponds to the basal nucleus of Meynert [319, 704, 912]. This nucleus consists of smaller or larger groups of neurons, which are embedded within the substantia innominata [488, 1189]. The cell groups are surrounded by islands of acetylcholinesterase-positive neuropil [1069]. The substantia innominata is a vaguely defined area situated ventral to the globus pallidus (Figs. 90–92). In rodents many of the large cholinergic neurons are situated within the portion of the substantia innominata defined as the ventral pallidum, but in primates the neuronal populations of the ventral pallidum and the basal nucleus appear to be less intermingled. At least 90% of the neurons in the basal nucleus are cholinergic. In the human brain, cell-group Ch4 contains approximately 200000 neurons in each hemisphere [51]. According to Mesulam and his associates [905, 906] the cholinergic neurons which constitute Ch4 can be separated into five subgroups: anteroventral (Ch4 av), anterolateral (Ch4 al), intermedioventral (Ch4 iv), intermediodorsal (Ch4 id) and posterior (Ch p).

The cell groups Ch1–Ch4 give rise to the following cholinergic projections:

1. Fibres originating from Ch1, Ch2 and Ch3 pass via the stria medullaris and the habenulointerpeduncular tract to the base of the midbrain, where they terminate in the interpeduncular nucleus and in the ventral tegmental area [346]. Cholinergic fibers contained in the stria medullaris also project heavily to the medial habenular nucleus, but whether the same or different populations of cholinergic neurons innervate the habenula and the ventromedial mesencephalon has not yet been determined.

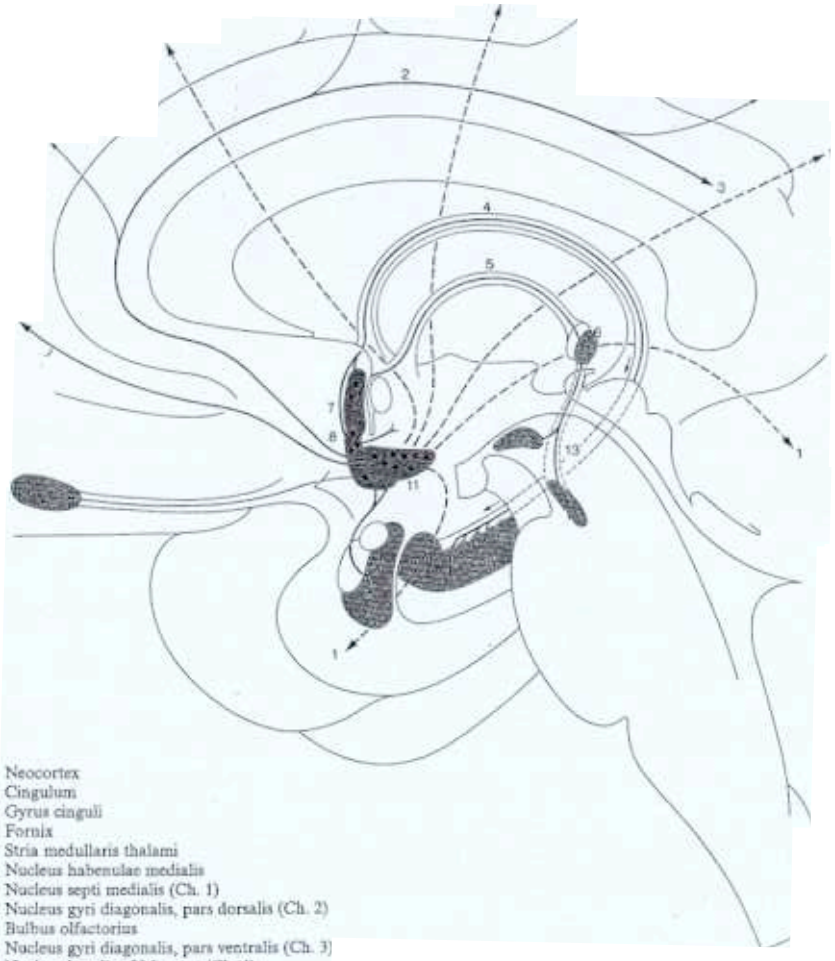
2. Ch1 and, particularly, Ch2 provide a substantial cholinergic projection to the hippocampus, as has already been suggested by Lewis and Shute [785a]. The fibres pass through the fornix and terminate in the cornu ammonis as well as in the fascia dentata [696].

3. Ch2 also sends fibres to the lateral hypothalamic area.

4. Cholinergic neurons situated mainly in Ch3 pass to the olfactory bulb, to terminate in the external layers of that structure.

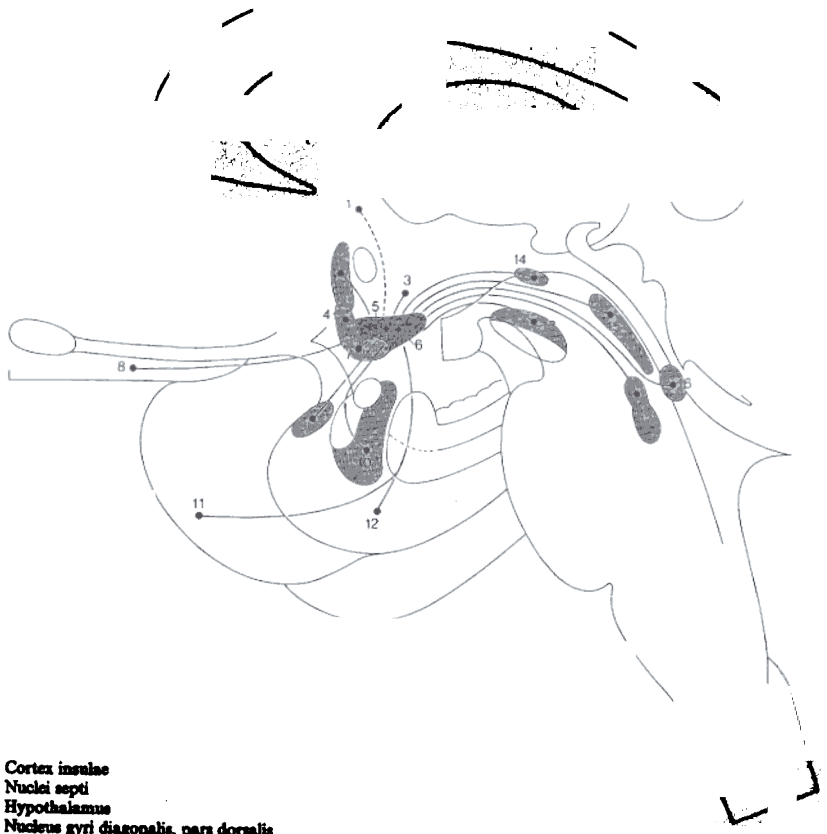
5. Cholinergic neurons located in the anterolateral portion of Ch4 project, via the ventral amygdalofugal pathway, to the amygdaloid complex, mainly to the basal nucleus [696].

6. The remaining parts of Ch4 provide a major cholinergic projection to the entire neocortex [118, 305, 623, 683, 771, 904, 906, 910, 925, 1063, 1246]. There is a specific but overlapping topography in the organisation of this projection. Ch4 am is the major source of projections to the medial surface of the hemispheres, including the cingulate cortex. Ch4al projects to the frontoparietal cortex, Ch4i to the prefrontal, lateral peristriate, middle temporal and inferotemporal regions, and Ch4p to the superior temporal gyrus and the temporal pole region [904, 906]. The routes along which the efferent of the basal



1 Neocortex
2 Cingulum
3 Gyrus cinguli
4 Fornix
5 Stria medullaris thalami
6 Nucleus habenulae medialis
7 Nucleus septi medialis (Ch. 1)
8 Nucleus gyri diagonalis, pars dorsalis (Ch. 2)
9 Bulbus olfactorius
10 Nucleus gyri diagonalis, pars ventralis (Ch. 3)
11 Nucleus basalis of Meynert (Ch. 4)
12 Area tegmentalis ventralis
13 Tractus habenulointerpeduncularis
14 Nucleus interpeduncularis
15 Fascia dentata
16 Cornu ammonis
17 Nuclei basales amygdalae

Fig. 180. Efferent connections of the magnocellular basomedial telencephalic comple



1 Cortex insulae
2 Nuclei septi
3 Hypothalamus
4 Nucleus gyri diagonalis, pars dorsalis
5 Nucleus basalis of Meynert (Ch.4)
6 Substantia innominata
7 Nucleus gyri diagonalis, pars ventralis
8 Cortex orbitofrontalis
9 Cortex prepiriformis
10 Nuclei basales amygdalae
11 Cortex temporalis polaris
12 Cortex entorhinalis
13 Substantia nigra, pars compacta
14 Nucleus peripeduncularis
15 Nucleus raphes dorsalis
16 Locus coeruleus
17 Nuclei parabrachiales

Fig. 181. Afferents of the nucleus basalis

nucleus reach the cortex have been studied in rat [1189], cat [1389] and monkey [696].

Without going into details, fibres forming a medial pathway enter the cingulum bundle and innervate the cingulate gyrus as well as dorsal and medial aspects of the cortex, whereas fibres assembling in a lateral pathway enter the external capsule, fan out within the corona radiata and are distributed to lateral parts of the parietal, occipital and temporal cortices. The medial and lateral pathways have also been observed in the human brain [1189]. The cholinergic innervation of the cerebral cortex shows considerable regional variations in laminar distribution and intensity. This innervation is particularly prominent in the caudal orbitofrontal cortex, the cingulate gyrus, the insula, the parahippocampal region and the temporal pole [909].

The basal nucleus has been suggested to represent a telencephalic extension of the reticular formation of the brain stem [904, 910]. It receives afferents from a variety of cortical and subcortical sources [475, 594, 631, 776, 902, 904, 1004, 1103, 1168, 1196]. The cortical input arises from the prepiriform cortex, the orbitofrontal cortex, the anterior insula, the rostroventral temporal cortex and the entorhinal cortex. Thus, in contrast to its widespread projections to all parts of the neocortex, the basal nucleus receives reciprocal projections from only a relatively small number of cortical areas. The subcortical afferents of the basal nucleus originate from: the septal nuclei; the nuclei of the diagonal band; the accumbens nucleus – ventral pallidal complex; the amygdala, particularly the basal nuclei; the hypothalamus; the peripeduncular nucleus; the pars compacta of the substantia nigra; the mesencephalic raphe nuclei; the parabrachial nuclei; and the locus coeruleus. Considering its afferents, Mesulam and coworkers [904, 905] considered it likely that the Ch4 complex acts as a cholinergic relay between limbic plus paralimbic areas and the entire neocortex in a fashion that may influence complex behaviour according to the prevailing emotional and motivational states. Russchen, Amaral and Price [1168] pointed out that although the structures which project to the basal nucleus are remarkably disparate, virtually all of them are integrative regions or regions of polysensory convergence. This holds in particular for the amygdala, which is itself organised to sample inputs from a variety of cortical, limbic and subcortical structures. The amygdala, which projects massively to the basal nucleus, is believed to play a role in evaluating whether incoming sensory information is of relevance to the individual, in relation to previous experience or to other inputs from the external or internal environment. Russchen and colleagues [1168] consider it likely that the integrated sensory input which the amygdala and other areas of the brain provide to the basal nucleus leads to activation of the cholinergic inputs to the cerebral cortex, and that this activation modulates cortical activity such that relevant sensory inputs lead to integrated motor or emotional responses, or to learning and memory.

The basal nucleus and its cholinergic cortical projections have attracted considerable interest recently because these structures have been implicated in the pathogenesis of Alzheimer's disease (AD) and its variant in the elderly, senile dementia of the Alzheimer's type (SDAT). In this disease the amounts of choline acetyltransferase and acetylcholinesterase, i.e. the enzymes which are responsible for the synthesis and the inactivation of acetylcholine, are considerably reduced in the cerebral cortex [284] and the cholinergic neurons in the basal nucleus undergo a profound and selective degeneration [333, 879, 880, 1499, 1500]. Whether this loss of cells is due to a primary lesion of the perikarya or rather represents a retrograde phenomenon, following degeneration of the widespread cortical projections and terminals of the basal nucleus neurons, has not yet been determined [50, 51, 901].

It is worthy of note that in AD/SDAT some other centres which project directly to the cortex, namely the noradrenergic locus coeruleus [142, 847, 856], and the largely se-

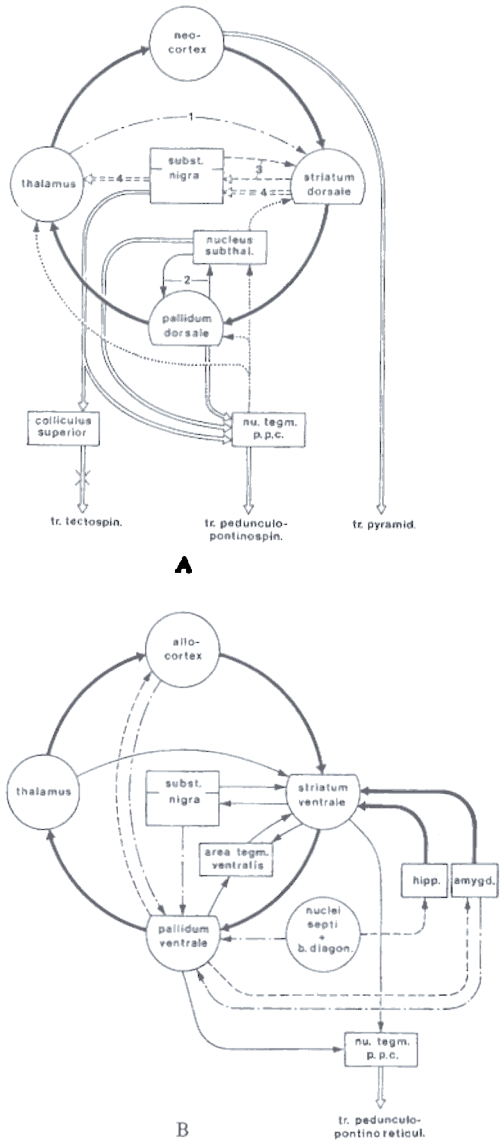


Fig. 182 A, B. Summary of the so-called extrapyramidal motor system. **A** the circuitry related to the dorsal striatum; **B** the circuitry related to the ventral striatum. In A the *bold arrows* represent the main extrapyramidal circuit and the *numbers* indicate the four accessory circuits described in the text

rotonergic dorsal raphe nucleus [275, 1498, 1533] are also affected, while at the same time such cholinergic cell groups as the large striatal local-circuit neurons and the somatic and visceral motoneurons in the brain stem and spinal cord are spared. Finally, it should be mentioned that a considerable loss of neurons in the basal nucleus of Meynert, accompanied by a deficiency of the cholinergic cortical projection system, is seen not only in AD and SDAT, but also in other disorders with similar deterioration of memory and cognitive functions, like Creutzfeldt-Jakob's disease [50a], Korsakoff's disease [49], many cases of Parkinson's disease [49, 968, 1141, 1498], and the remarkable Parkinsonism-dementia complex of Guam [967].

Descending Reticular Systems

Descending Projections from the Raphe Nuclei
(Fig. 183)

The pathways which descend from the raphe nuclei may be categorised as:

1. Projections terminating in rhombencephalic centres
2. Raphespinal projections.

The former have been visualised mainly on the basis of the serotoninergic character of their constituent fibres and will be designated accordingly. The raphespinal projections contain many non-serotoninergic fibres [1258].

Serotoninergic Projections to Rhombencephalic Centres. The detailed mapping study of Steinbusch [1288] has shown that in the rat a great number of rhombencephalic centres receive serotoninergic innervation. Substantial numbers of serotoninergic fibres and terminals have been observed in the following cell masses: the principal sensory nucleus and spinal nucleus of the trigeminal nerve, the solitary tract nucleus, the locus coeruleus, the pontine central grey matter, the parabrachial nuclei, the dorsal tegmental nucleus, the nucleus prepositus hypoglossi, the pontine and medullary reticular formation, the raphe nuclei and most of the somatic and visceral motor nuclei. Little is known of the specific sites at which the serotoninergic projections to all of these centres originate. However, it has been established that the locus coeruleus receives a large projection from the dorsal raphe nucleus [134, 225, 252, 949, 1180, 1350] and that the dorsal raphe nucleus and the central superior nucleus send fibres to the dorsal tegmental nucleus, the pontine central grey matter, the rhombencephalic raphe nuclei and the pontine and medullary reticular formation [133, 134, 1544]. Similarly, the pontine raphe nucleus and nucleus raphes magnus project to the reticular formation [134].

The raphespinal projection is constituted by fibres that arise principally from the raphes magnus, raphes pallidus and raphes obscurus nuclei [148, 1402]. In the spinal cord most of these fibres descend in the superficial zone of the anterior and lateral funiculi [149, 280], with distinct concentrations in the dorsal part of the lateral funiculus and in the medial part of the anterior funiculus [501]. The raphespinal fibres terminate preferentially in the superficial layers of the dorsal horn, the intermediolateral cell column and in the regions containing somatomotor neurons [280, 1288].

According to Skagerberg and Björklund [1258] the raphespinal projection comprises three pathways, dorsal, intermediate and ventral. The dorsal pathway, which contains a large non-serotoninergic component, arises principally from the nucleus raphes magnus, descends through the dorsal part of the lateral funiculus and terminates mainly in the superficial dorsal horn at all spinal cord levels. The intermediate pathway is largely serotoninergic, with its cell bodies located in the raphes obscurus and raphes pallidus nuclei, particularly in the superficial ventrolateral extension of the latter, and terminates mainly in areas of preganglionic autonomic motoneurons at thoracolumbar and upper sacral levels. The ventral pathway consists of sero-