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The Basal Ganglia-Circa 1982

A Review and Commentary[1]

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Abstract. Our review has shown that recent studies with the new anterograde and retrograde axon transport methods have confirmed and extended our knowledge of the projection of the basal ganglia and clarified their sites of origin. They have thrown new light on certain topographic connectional relationships and revealed several new reciprocal connections between constituent nuclei of the basal ganglia. Similarly, attention has been drawn to the fact that there have also been many new histochemical techniques introduced in recent years that are now providing regional biochemical overlays for connectional maps of the central nervous system, especially regions in, or interconnecting with, the basal ganglia. However, although these new morphological biochemical maps are very complex and technically highly advanced, our understanding of the function controlled by the basal ganglia still remains primitive.

The reader who is interested in some new ideas of the functional aspects of the basal ganglia is directed to *Nauta's* [88] proposed conceptual reorganization of the basal ganglia telencephalon and to *Marsden's* [72] more clinically orientated appraisal of the unsolved mysteries of the basal ganglia participation in the control of movement.

Introduction

When we were asked to write this review in 1980, we thought it would be a simple matter of updating a previous review [79]. We had continued to investigate interconnections of certain basal ganglia compo-

[1] Keynote address of the Meeting of the American Society for Stereotactic and Functional Neurosurgery, Houston, Tex., 1980.

nents such as the substantia nigra [20] and the amygdala [78] and to sample the current literature on other structures. When we assembled this post-1974 collection of reprints, the pile exceeded several thousand printed pages, perusal of which indicated that we had overlooked at least an equal number of pages in the ensuing 6 years on the anatomy and physiology of the basal ganglia. Reviews by *Dray* [16] and *Grofova* [34] on the corpus striatum alone contain over 400 literature citations. Since these recent papers along with major reviews by *Carpenter* [4] and *Graybiel and Ragsdale* [28], contain comprehensive bibliographies up through 1978, we have curtailed references chiefly to more recent papers and to older studies relevant to our commentary, particularly studies of the primate brain.

We have previously drawn attention to the fact that periodic advances in our understanding of the neuroanatomical organization and function of the brain arise chiefly from the introduction of new investigative techniques [75, 77]. In these reports we traced the history of the discoveries of certain major brain pathways from the Marchi and Golgi methods period at the turn of the twentieth century through to the Nauta-silver-methods period in the 1950s and 1960s that culminated with the introduction of the very sensitive *Fink and Heimer* variants in 1967. These techniques created a renaissance in neuroanatomy and they continue to be of value when used in conjunction with other new techniques. The introduction and rapid refinement of the axon transport methods in the early 1970s ushered in yet another new era in the discovery of unknown interconnections of parts of the brain and refinements in the precise cell origins and axon terminations of many known pathways. The latter methods utilize autoradiographic demonstration of anterograde axon transport of injected tritiated amino acids (TAA) incorporated by cells [10] or the retrograde transport of the enzyme horseradish peroxidase (HRP) picked up chiefly by nerve terminals in the area of injection [66].

The corpus striatum, globus pallidi, amygdada, and claustrum are the four major forebrain cell groups that constitute the basal ganglia in a strict morphological sense. With the exception of the claustrum, the other three are subdivisable into regional parts: the striatum into a part with a tail (L. caudatum) and a part cut off from the caudate by the internal capsule, the putamen (L. for a cutting or paring); the globus pallidus into lateral and medial segments, and the subadjacent amygdala into a number of cytologically distinct subnuclei. Based upon evidence of interconnections of the striatum and globus pallidus with each other and with certain nu-

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clei in the diencephalon and mesencephalon (such as the subthalamic nucleus and the substantia nigra), the term 'basal ganglia' is often expanded to include all of these noncortical structures because of their interconnections and their combined involvement in pathological conditions underlying movement disorders.

The Corpus Striatum

The caudate and putamen divisions of the corpus striatum are cytologically homogenous in Nissl sections; both parts contain chiefly medium-sized achromatic cells (12–18 μm) and large scattered metachromatic cells (20–30 μm) in proportions estimated from 20:1 to 150:1. Golgi studies suggest that there are at least two distinct types of cells, 'spiny' and 'aspiny'. The generally smaller aspiny types have short axons like the classic Golgi type II cell; the spiny type, which have long axons, may be small or large bodied. Actually, the majority of the small cells that have long axons (identified as spiny type II) appear to be the chief striatofugal cell type that projects to the pars reticulata of the substantia nigra. Classification of the diffusely distributed 'large' chromatic cells that are evident in Nissl sections is still controversial and new evidence suggests that there might even be two different classes of large cells [101].

Striatal *afferent* connections originated from at least five sources: cerebral cortex, thalamic intralaminar nuclei, the pars compacta of the substantia nigra and associated paranigral dopaminergic cell groups, the mesencephalic raphe nuclei, and the locus ceruleus.

The *corticostriate* projection, which originates from layer V of the cortex [50], distributes topographically but with variable intensities of partially overlapping connections over all parts of the striatum. There is a rather limited occipital projection to the tail of the caudate but the precentral 'motor' cortex, for example, projects in a somatotopic fashion chiefly upon the putamen (dorsal to ventral: leg, arm, face). The supplemental 'motor' and 'sensory' regions appear to distribute bilaterally [53, 54, 60, 62]. *Liles* [67] recorded evoked potentials in the striatum from cortical stimulation and he found almost total, somatotopically organized overlap of the pre- and postcentral cortices in the putamen of the monkey.

Thalamostriate connections that originate from the centrum medianum and parafascicular nuclei and intralaminar nuclei, such as the central

lateral complex and the paracentralis, have been known for many years [76, 103]. The new methods have confirmed these connections and have introduced data suggesting that cells in certain of the so-called midline nuclei of the thalamus, such as the centralis inferior (or medialis), also project to the striatum in the cat [110, 111] and monkey [*Mehler*, unpubl.].

There is growing evidence that the *nigrostriatal* projection originates from several other paranigral dopaminergic cell groups in the ventral tegmental region of the mesencephalon, in addition to those from the pars compacta (see 'Substantia nigra' discussion). *Kitai* et al. [57, 58] have shown that excitatory cells in the nigra, intralaminar nuclei and cortex converge monosynaptically on striatal projection cells that can be characterized by antidromic stimulation of the nigra and demonstrated anatomically by microinjection of HRP into the striatal cell being recorded. The striatal distribution of projections from mesencephalic raphe neurons and cells in the locus ceruleus appear to be individually widespread and overlapping. The raphe nuclei contain neurons that are the major source of serotonin projections to the striatum and other forebrain areas and the locus, adrenergic projections to much the same region [85].

The chief target of the efferent projections from most of the medium-sized cells in striatum is the substantia nigra, pars reticulata (SNr). The complete history of this quest, from *Edinger*'s surmise in the 1900s up to *Voneida*'s [117] anterograde fiber degeneration studies demonstrating striatonigral connections, has been published [34, 92]. They have been verified in electron microscope studies [108] and recent HRP studies in several species have shown that these axons originate from the smaller striatal cells alone [19, 20, 34]. Both fiber degeneration and Golgi studies suggest profuse short collateral connections with cells in the pallidal segments, as the striatonigral fibers converge through the apical segments of the lentiform nucleus in their descent to the nigra [23, 92].

In the 20 years that we have been involved in studying the connections of the basal ganglia, one of the most elusive problems has been the connections of the large striatal cells. In 1920, *Vogt and Vogt* [116] hypothesized that the large cells were the major source of striatofugal axons and that the small cells were probably the major source of intrinsic receptors. The suggestion of *Mettler* et al. [81] that these large cells might project to the cortex (i.e., a possible source of the recruitment phenomenon) was an attractive idea. Initially, HRP cortical injection studies did not appear to support the idea. *Jayaraman* [48], however, has just reported the

appearance of HRP-labeled large cells (30–60 μm) in the striatum after large HRP injections in the auditory cortex in the cat and a few also after a nonauditory cortical injection, suggesting a topological distribution of such cells in the striatum that might have obscured the identification of these striatocortical projections in the earlier HRP studies. This observation, however, remains to be verified. Recently, *Kemp and Powell* [54] concluded, as the *Vogt and Vogt* [116] had done, that these large cells were the chief source of striatonigral fibers and that the surrounding medium and smaller cell types were interneurons. The massive volume of the striatonigral fiber projection, even after small striated lesions, however, should have mitigated against this conclusion. HRP studies have since clearly demonstrated that it is only cells of the smaller spiny type II striatal cell type that label after HRP injections into the SN pars reticulata, as has already been noted.

During the course of our HRP study of amygdala afferent connections [77], several injections impinged on the globus pallidus. In one case (SqM 10-R) the lentiform nucleus was penetrated and the major focus of HRP was deposited in the medial segment of the globus pallidus (MGP). Search of the striatum in this case revealed numerous labeled small cells and *also* a number of the large cells. Collaterals to both the medial and lateral segments of GP from the small-celled striatonigral projections that converge through the pallidus are believed to exist [92], which explains the widespread, small-celled labeling that normally occurs after nigral HRP injections alone [20]. Initial analysis indicates that the labeled large cells in this case measure from 15×30 μm up to 20×40 μm (short vs. long axis). Whether they are the classical metachromatic 'giant' cells or the rare, large, spiny type II, described by *DiFiglia* et al. [15], is presently unknown, because the HRP incorporated in the soma masks the Nissl material and, to date no large labeled cells have been found with adequate dendritic retrograde HRP filling to produce a pseudo-Golgi image that can be classified along the latter line of study. These findings, suggesting that large cells in the striatum probably are efferent to cells in the MGP, are schematically illustrated in figure 1.

Attention should be drawn to the histochemical studies of acetylcholinesterase (AChE) activity in the basal ganglia by *Parent* and co-workers. Comparative anatomical studies of AChE-rich structures in the forebrain by *Parent and Olivier* [98] demonstrated trans-specific correspondence in the distribution of AChE throughout the corpus striatum (including accumbens) in the turtle, pigeon, rat, cat, and monkey. In a later study in

monkeys utilizing pharmacological manipulation that depletes AChE in axons and terminal processes, they found that *only* the randomly distributed large striatal cells and the short axoned 'spidery' cells of *Fox* et al. [23] actually are AChE positive; the usual background neuropil AChE staining apparently originates largely from afferent cell sources outside of the striatum [102]. Known striatal afferent cell groups, such as the nucleus parafascicularis and cells of the intralaminar nuclei, for example, show intense AChE activity in such treated brains, but the cells of the nucleus centrum medianum interestingly show low AChE cell activity [100].

In a series of papers, *Graybiel and Ragsdale* [27–29] have methodically examined asymmetrical three-dimensional compartmentalization 'units' that can be demonstrated in the striatum. These geometrically complex islands in the striatal archipelago were suggested by an astute combination of observations by these investigators (cloudlike autoradiographic striatal afferent terminations and variably shaped noncell labeled regions in the dense matrix of retrogradelabeled striatal cells found after HRP injections into the nigra) and most vividly demonstrated by AChE histochemistry in experimental animal and human brains. The reader is referred to *Graybiel and Ragsdale*'s [28] comprehensive review of this important discovery and their discussion of histochemical data bearing on the possible relationship of these paler striatal 'islands', or AChE-weak tubular bodies to the maturation of various striatal afferent systems like the dopaminergic nigrostriatal system [29].

These authors note that years ago (in 1929), *Papez* [96] described 'tubular clusters' in the striatum similar to the islands or bodies of 'striosomal organization' (their new term) that they are investigating. It would be interesting to compare the sizes of the *striosomes* with the amyelinated lacunae in the striatum of brains identified as in the pathological conditions of *état marbré* and/or *état fibreux* [116]. These pale staining compartments among the marble-like veins of myelinated fibers have been noted to contain residual 'large' cells accompanied by a conspicuous reduction of surrounding small cells in the brain of a child with a history of birth injury [94].

It is evident that these striosomes probably represent some kind of functional unit. They are surrounded by cells giving rise to the massive striatonigral projection and are described as roughly 0.5-mm wide zones that may be up to two or three times longer in a given cross section. The largest striatal cells in the monkey described in Golgi sections by *DiFiglia* et al. [15] had dendritic radii of 250 μm or a diameter of 0.5 mm. *Kitai*

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[pers. commun.] also has found a large HRP labeled cell in the cat's striatum with a dendritic diameter just over 0.5 mm. Is it possible that one or several of these diffusely distributed large cells occupy the core of these striosomal units and are packed in clusters of some yet to be identified non-nigra projecting, histochemically specific, striatal small cell types? *Greybiel* et al. [32] have already found enkephalin-rich patches in the cat's striatum that are in register in alternate sections with the AChE-poor striosomes. They also found reasonable overlap in substance P patches but somatostatin-positive cells were localized chiefly in the striatal matrix surrounding the striosomes. *Ragsdale and Greybiel* [105] also have some correspondence in the distribution of corticostriate connections with the striosomes but not total registration.

Graybiel et al. [31] considered the possibility of the large cells being present in these units after pallidal HRP injection experiments in the cat, but rejected the idea in the absences of unequivocal matching of HRP labeled large cells and large metachromatic cells in the same slide restained with a Nissl stain. While I do not consider my evidence of labeled large cells in the striatum after MGP injections as unequivocal, and the striosome zones are not that clear in our monkey material up to this date, the idea is well worth some speculative consideration and further investigation.

The Globus pallidus

The *lateral* segment of the globus pallidus (LGP) is situated between the putamen and the apical, medial pallidal segment of the lentiform nucleus. It is composed of medium-sized neurons, many of which have spindle-shaped soma whose polar dendrites extend perpendicular to the striatofugal fiber outflow converging through LGP. Cells with this polarity are best seen in Nissl or Golgi horizontal sections and occasionally in coronal sections through the rostral part of LGP. Reviewing Weil-stained monkey brains, we found a previously undescribed myelinated, dorsoventral linear fiber plexus in LGP that also runs perpendicular to the striatofugal projections passing through the pallidi. In our experimental excursions through the forebrain, we have not seen any evidence suggesting the origin of these plexus fibers. *Nauta and Cole* [89], however, have reported reciprocal subthalamic nucleus projections to both the lateral and the medial segments of GP that terminate in several 'bands' that they de-

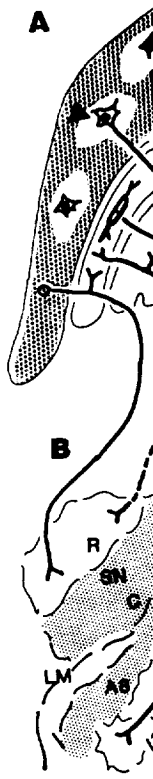
scribed as being orientated 'parallel to the medullary lamina separating the segments' that might correspond to the myelinated plexus in question.

The major efferent target of the LGP is still the subthalamic nucleus. *Grofova* [33] and *McBride and Larsen [74]* ascribe to projections from LGP to nigra, based upon HRP injections into the pars reticulata of the nigra in cats, and both *Kim* et al. [56] and *Nauta* [87] also guardedly suggest LGP anterograde projections to SNr, especially its *pars lateralis*, following TAA injections. In addition to short striatofugul fiber collateral afferent connections and reciprocal subthalamic nuclear projections [6, 89], *Lindvall and Bjorklund* [68] have described a sparse but demonstrable dopaminergic plexus of collaterals distributing to LGP from the ascending pars compacta nigrostriatal system.

The *medial* globus pallidus (MGP) in man and the higher primates is often further subdivided into internal and external parts by an incomplete fiber lamina, both of which nevertheless contain cells slightly larger than those in LGP. Afferent connections with MGP originate chiefly from the striatum and from the subthalamic nucleus [6, 89]. The MGP alone gives rise to the pallidothalamic projection that distributes to the parvocellular part of the ventral anterior nucleus (VApc=LPo), the oral subdivision of the ventralis lateralis nucleus (VLo=Vo), the nucleus centrum medianum (CM) and a long projection to the nucleus tegmenti pedunculopontinus pars compacta (Tgc) located in the caudal mesencephalon (fig. 1). This pattern of MGP connections, first fully established in fiber degeneration studies by *Nauta and Mehler* [92], has been confirmed by autoradiographic method analyses in the monkey [56] and cat [87].

Kuo and Carpenter [63] analyzed the topographic distribution of pallidothalamic fibers in a series of 21 monkeys with different MGP lesions. They concluded that the *rostral* MGP cells terminate predominantly in VApc and those in the caudal part of MGP terminate in VLo. Their analysis of variously placed lesions in MGP also suggested that there might be external MGP to lateral VL-VA and internal MGP to medial VL-VA thalamic topographic relationships and some evidence of preferential dorsal MGP to dorsal VL-VA nuclear regions and ventral MGP to ventral VL-VA thalamus projectional organization.

It might be profitable to examine MGP in a large number of brains of cerebrovascular accident cases with respect to these suggested differences in internal and external MGP projections to see if any functional differences might be discovered in those patients with *selective* MGP cerebrovascular lesions and minimum involvement of the internal capsule.



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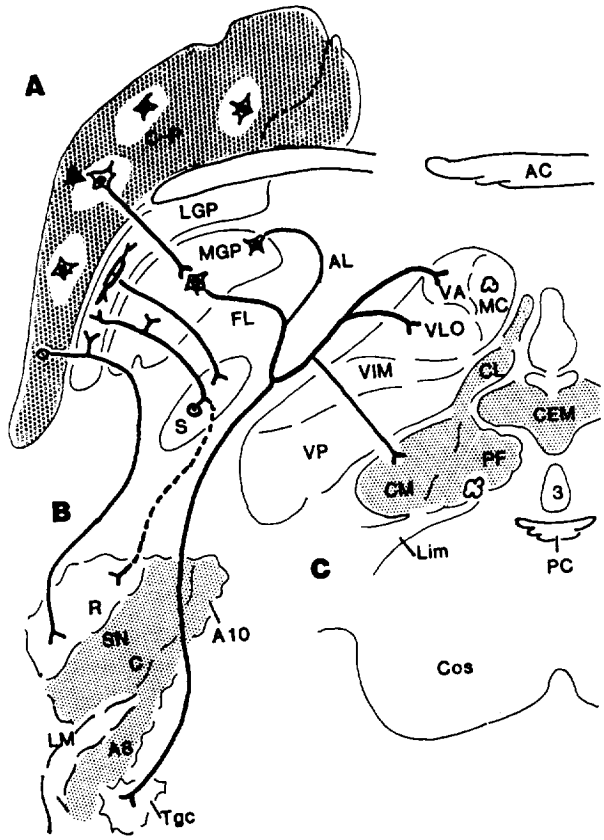

Fig. 1. Semischematic drawing of basal gangliar structures and the dorsal thalamus abstracted from three levels of a squirrel monkey brain cut in the horizontal stereotactic plane showing relative sizes of interconnected constituent nuclei. **A** Efferent connections of the caudate nucleus and the putamen (C-P), lateral (LGP) and medial (MGP) globus pallidus, subthalamic nucleus (S), ansa lenticularis (AL), fasciculus lenticularis (FL). Arrowhead: hypothetical organization and connection of 'striosoma' (see text). **B** Substantia nigra (SN), pars reticulata (R) and pars compacta (c), nucleus pedunculopontinus, pars compacta (Tgc). Shaded areas SNC (A9) and contiguous tegmental areas A8 and A10 that contain monominergic (DOPA) cells which project to the corpus striatum. **C** Dorsal thalamus and superior colliculus (Cos). Shaded intralaminar nuclei centralis lateralis (CL), centrum medianum (CM), centralis medialis (CEM), parafascicularis (PF) that also project to the corpus striatum.

Ventral tier nuclei: posterior (VP), intermedius (VIM), lateralis pars oralis (VLO) anterior (VA) and its pars magnocellularis (MC). Nucleus limitans (Lim). Iter of third ventricle (3), lemniscus medialis (LM).

DeLong [12] for example, noted that units in *both* pallidal segments of the monkey that responded to rapidly alternating movements of the limbs were concentrated in the *external* parts of LGP and MGP, suggestive of some intrapallidal specialization. He also found that the 'leg' units tended to be grouped dorsal to the 'arm' related units in the pallidi, consistent with current anatomical notions of dorsiventral (leg, arm, face) somatotopy in the putamen.

If such individual topological relationships exist between MGP and the rostral part of the thalamus, they might portend subtle functional differences between the two differential sets of pallidothalamic connections that could have useful clinical significance apropos of stereotactic intervention. Although Vim, which does *not* receive pallidal input, is still the target of choice for relief of tremor, the best site for placement of stereotactic lesions in the VL complex for the relief of rigidity is still questioned by *Hassler* et al. [40].

The Nucleus basalis

There have been reports that the nucleus basalis projects to the pars compacta of SN, to the lateral habenula and to the cerebral cortex. A review of the data supporting these connections follows. Some comments are included on the controversy surrounding the question of whether medial pallidal segment cells or cells in the nucleus basalis project to the habenula. These new data are the first evidence concerning the connectivity of this large enigmatic cellular mass dispersed throughout the region ventral to the globus pallidus.

The *nucleus basalis* of Meynert should be mentioned because of its intimate relationship with the lentiform nuclei. These large, metachromatic cells, sometimes found to contain lipofucsin, lie chiefly dispersed in the *substantia innominata* ventral to the pallidal segments. There are also large numbers of these cells scattered throughout the lamina separating the putamen from LGP. They are especially numerous in the lamina between the pallidal segments, which extends from the region just rostral to the lateral geniculate body to the base of the fundus striati. They are AChE-positive; pallidal cells are not [99].

Kim et al. [56] suggested (TAA method) that these basalis cells *might* be the origin for the still uncertain afferent connections of SN *pars compacta* (SNc). Reviewing our earlier pallidal lesion cases we find that ex-

periment MGB-7 [92], with an almost horizontally angled electrolytic lesion centered chiefly in the dorsal part of the innominata, produced the most convincing fiber degeneration in our series of experiments that looked as if basalis cells might terminate in SNc and, as we now understand, also in the retrorubral dopaminergic A8 nucleus. We rejected this idea of a 'basalis-SNc' connection at the time because of the innate problem of interpreting preterminal fiber degeneration in a nucleus like SNc in monkeys where the cell pigment is normally argyrophilic. This endogenous pigment 'pseudo-positive' problem continues to plague us to some degree in interpreting the results in experiments with both of the new axons transport methods.

Nevertheless, HRP injections into the SNc region have not revealed confirmatory cell labeling in nucleus basalis in either the cat or monkey in our laboratory.

This particular 'basalis' lesion in our MGB-7 experiment also produced intense projections to the lateral habenular nuclei, but since we found significant habenular connections in lesions restricted to the MGP we *suggested* that a pallidohabenular projection might be found. *Nauta*'s [86, 87] autoradiographic studies of entopeduncular (the feline MGP) projections supported the latter idea, but the evidence of *Kim* et al. [56] (TAA) led them to conclude that the habenular afferent connections probably originated from the basalis cells in the monkey.

Herkenham and Nauta [42], by placing minute injections of HRP into the lateral habenular nucleus of the rat, labeled a continuum of cells from the substantia innominata through the anterior part of the lateral hypothalamus and throughout the entopeduncular nucleus (the rodent's MGP). *Larsen and McBride* [64] analyzed the cat's entopeduncular nucleus (Ento) with the new methods and concluded that Ento cells projecting to the habenula were distributed throughout the nucleus. They noted, however, that the number of HRP-labeled cells found in the Ento were much fewer than those observed in HRP injections into the ventral anterior nucleus (VA) of the thalamus and that the population of Ento cells projecting to the habenula in the cat was much smaller than *Herkenham and Nauta* [42] had found in the rat. They noted that this more restricted Ento-habenular projecting cell population was consistent with data obtained in a previous neurophysiological study of antidromic discharges, induced by stimulation of VA, CM, or the lateral habenula. This study, however, also suggested that the cells projecting to the habenula were

concentrated around the rostral pole of Ento and in the medial part of Ento caudally [65].

Parent et al. [99] demonstrated a pattern of distribution of strongly AChE staining basalis-type cells in the substantia innominata (SI), lateral hypothalamus and *peri*pallidal regions of the rat, cat, and monkey: they noted that some of these AChE cells do invade the entopeduncular nucleus at its rostral and caudal poles in the rat, a few were found in the region ventral to Ento in the cat, but they were restricted chiefly to the pallidal lamellae in the monkey. The adjacent lateral hypothalamic and other specified regions in all three species *also* contained large numbers of AChE-positive cells.

Parent [97] followed up on these histochemical studies with habenular HRP injection experiments in monkeys that revealed cell labeling restricted to the contiguous *peri*pallidal regions of the lateral hypothalamus and the basalis-type cells in the lamina separating MGP from LGP. Conversely, in VA-VL thalamic HRP control experiments, labeled cells were found only in the medial pallidal segment from which the pallidothalamic fasciculus originates. *Parent* [97] concluded that these data suggest significant quantitative and qualitative species differences in the distribution of the cells of origin of the so-called pallidohabenular connection in the rat and monkey. Other afferent and efferent connections of the basalis cells tend to support exclusion of the peripallidal cells from the MGP per se and suggest other functional relationships.

Jones et al [51], for example, traced projections (TAA method) from the peripeduncular nucleus [47] to the lateral amygdala and to the basalis cells in the pallidal lamina and the substantia innominata. They (and others) also found that a number of these basalis cells could also be labeled retrogradely by HRP injections into the cerebral cortex, especially area 4 [55]. It is not yet known whether the same HRP and basalis cells project to both the cortex and the habenula. The question still remains whether there is really a pallidohabenular connection in primates or only a basalis-to-habenula projection functionally unique and separate from MGP cells that give rise to the more massive pallidothalamic connections. Double cell marker experiments that *Parent* [97] has suggested might resolve this problem.

In rats, cats and a monkey with HRP injections involving the habenula [*Mehler and Phelan,* unpubl.] the patterns of labeled cells in the pallidal structures appear remarkably similar to the AChE cell distribution described by *Parent* et al. [99]: some labeled cells in the rat's Ento,

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HRP-positive cells chiefly in the ventral edge of the cat's Ento and labeled cells restricted to the peripallidal lamina in the monkey. On the other hand, in several cat and monkey experiments with small, pipette iontophoretic HRP injections apparently confined to Ento or MGP, dense, anterograde transported HRP could be found in the neuropil of the lateral habenula.

The story on the connections of the basalis complex obviously is still not complete. While this brief history of these studies may seem academic, the results outlined should remind the reader that even with new methods, the data obtained from the most carefully planned, executed and assiduously analyzed experiments can still be misleading because of apparent or real species differences or possible technical caprices indigenous to both older and newer experimental methods.

The Subthalamic nucleus

The cytoarchitecture of the *subthalamic nucleus* (STN) has been described by a number of authors. Recently, *Rafols and Fox* [104] described two varieties of principal cells and the presence of a Golgi type II interneuron in the STN of several species of monkeys. However, based on comparable Golgi studies, *Yelnik and Percheron* [118] argue against such a heterogeneous STN cell composition in favor of a homogeneous nucleus of Golgi type I neurons alone in the cat, the monkey, and in man. One would think that some new histochemical method might help to resolve this question. Until recently, there has been a conspicuous absence in the literature of histochemical data on the STN. Glycine, however, has been suggested as a neurotransmitter [119]. AChE activity is weak [102], but glutamic acid decarboxylase (GAD) has been identified in STN [22]. *Nauta and Mehler* [92] confirmed *Vogt and Vogt's* [116] earlier conclusions that STN received its main subcortical afferent input chiefly from the lateral GP. Autoradiographic studies have confirmed this idea [56], and *Hartmann-Von Monakow* et al. [36] have also shown that area 4 projects *somatotopically* to STN and areas 6 and 8 (axial musculature) topologically. There are some unresolved questions about afferent connections with the caudal pole of STN and other differences in this region [8]. The former, we believe, stems from the absence of any data on caudal lesions of LGP in the literature or from the possibility that the caudal pole in contaminated by atypical cells. In support of the latter notion

is *Meibach and Katzman*'s [80] histofluorescence evidence for a rostral continuation of SN pars compacta (A9) dopaminergic cells into the caudal pole of STN in the cat. In primate brains the caudal pole of STN actually overhangs the oral pole of the contiguous nigra.

The efferent ascending projections of STN go to both segments of the globus pallidus [89]. Although some controversy still surrounds the issue, anatomical anterograde and retrograde [89, 112] and neurophysiological data [13] now support the notion that the STN projects 'up' to GP and also 'down' to the ventral part of the *pars reticulata* of the substantia nigra. *Van der Kooy and Hattori* [114] have just shown by the use of a double retrograde marking technique that 94% of STN neurons in the rat project in both directions. Since the ascending STN-GP pathway is inhibitory and the descending STN fibers to SN apparently are collaterals of the same axon, then the subthalamic nucleus's influence on the nigra is probably also inhibitory. *Yoshida* [1194) has proposed a possible GABA or glycine-mediated inhibitory synapse in the STN-pallidal connection and *Larsen and Sutin* [65], who reviewed the pertinent neurophysiological literature on STN, have demonstrated definite *post*synaptic inhibition in entopeduncular nucleus cells (i.e., the MGP homologue) of the cat. These authors also note that the hyperkinesias that result from damage to STN in man and monkey have not been replicated in the cat.

Martin [73], who has appraised clinical features of subthalamic region pathology, and *Carpenter* [4] who has repeatedly studied the results of experimental lesions of STN, both have concluded that STN functions as a suppressor of pallidal output and that destruction of the STN on one side releases pallidal output and produces ballistic activity in the contralateral limbs. *Hammond* et al. [35] have experimentally induced a hemiballism and other hyperkinesias in a monkey with an injection of neurotoxic kainic acid specifically into STN on the side contralateral to the abnormal movements. *Modesti and Van Buren* [82] recently reviewed the incidence of hemiballismus with and without direct involvement of the subthalamic nucleus in stereotactic operations.

The Substantia nigra

Based upon studies with neuroanatomical methods, histochemistry, and advanced microelectrode neurophysiological techniques, there are considerable new data on the organization and connections of the sub-

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stantia nigra (SN). The substantia nigra is generally divided into a dorsal, cell-rich, dopaminergic, pars compacta ('black zone') and a ventral, less cellular, pars reticulata ('red zone').

In addition to cells in the larger-celled *pars compacta* (A9), dopaminergic cells also have been identified in both the nonprimate and primate A10-ventral tegmental area (Tsai's) and in the A8-supralemniscal, ventrolateral mesencephalic region. Both cell groups A10 (nucleus paranigralis) and A8 (nucleus parabrachialis pigmentosus), like the pars compacta, were known to contain melanin-like pigment in man [37, 95] and other primates long before they were identified as dopaminergic and enumerated as A10 and A8 on *Dahlstrom and Fuxe*'s [11] monominergic cell group list [84, 85]. Years ago, *Hassler* [37, 38] dubbed the combined pigmented cell groups as the 'black system' because he found this unification justified by the fact that *all* the pigmented cell groups were affected in one or another of the postencephalitic Parkinson's disease brains that he studied. Both the paranigral A10 and the ventrolateral tegmental A8 cells project chiefly to ventral striatal regions and A10, at least, also has connections with the amygdala in the monkey [78]. Both the A10 and A8 regions appear to receive fibers from the accumbens, the basilar 'limbic' part of the caudoputamen in the rat that appears to equate with the fundus striati of higher primates [17, 93].

The pars compacta is the major source of dopaminergic, nigrostriatal afferent connections [1]. In the rat and cat they ascend in the lateral part of the medial forebrain bundle (MFB) before they cross the internal capsule and terminate in the striatum. In primates, *however*, the initial course of nigrostriatal pathway does *not* traverse the lateral hypothalamus in the MFB, but, as *Carpenter and Peter* [5] clearly pointed out, these fibers ascend chiefly dorsal to the subthalamic nucleus in fields H2 and H of Forel in the subthalamic region.

The recognition of this shift in the ascending fiber 'channels' of the nigrostriatal projection, from the lateral MFB chiefly into the subthalamic region, could be very important to the stereotactic surgeon as well as the experimentalist. It probably reflects the tremendous enlargement in the volume of the pars compacta in the primate brain compared to that found in rodents and carnivores. In the rat and cat, for example, the A10 ventral tegmental area is almost as large as the pars compacta, while in the monkey the volume of the compacta is many times larger than that of the limbic system-related A10 cell group. One can cite a number of other neurological species differences that might affect this dramatic shift in the

course of the nigrostriatal pathway. The relative and actual increase in the size of the laterally situated putaminal part of the striatum in primates is one example. This change also can be correlated with the lateralization and tremendous enlargement of 'motor' cortical areas 4, 6, and 8 whose layer V corticostriate projections converge chiefly on the putamen [50]. There is also the expansion and consolidation of the primate *medial* pallidal segment (i.e., the nonprimate's entopeduncular nucleus) with the lateral GP and the putamen into a single, conical mass (i.e., the lentiform nucleus) whose combined efferent fiber discharge expands and remodels the subthalamic region in the primate brain. Last but not least, there are phyletic volumetric changes in the subthalamic and hypothalamic regions that are most evident in the expansion of the relative volume of the subthalamic nuclei and the relative decrease in the size of the hypothalamus in the primate brain compared with the proportions of these regions in nonprimate brains.

The nigrostriatal projection has been studied most intensively in the rat. Outstanding are *Fallon and Moore's* [17] studies which demonstrated in three planes (medial-lateral, dorsoventral and anterior-posterior) topography in the distribution of dopaminergic nigral and paranigral cell projections to the striatum. *Carpenter* et al.'s [5, 7] silver and autoradiographic studies of nigral projections and our data on nigral cell labeling patterns following different striatal HRP injections in the monkey suggest that there is essential conformity in the nigrostriatal connections in the monkey with the basic topographical patterns established in the rat. There still is no complete detailed map of these connections in the monkey; however, that would be more applicable to our understanding of the organization of these connections in the human brain.

The pars compacta also has some diffuse projections to the neocortex that were first suggested by *von Monakow* [83] in 1895, rediscovered by *Llamas* [69] in Nauta-method studies and subsequently have been confirmed to exist with the new methodology along with projections to limbic-related mesocortical areas [2, 17, 84, 91]. The endings of these nigrocortical projections, like the nigrostriatal connections, are dopaminergic. Those projecting to neocortical regions originate largely from cells in the more superficial strata of the pars compacta and those relating to the allocortex originate from dopaminergic cells in the A10, ventral tegmental area [2].

The major source of *afferent* connections of the pars compacta is still obscure. Several sources have been suggested in recent anterograde fiber

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transport autoradiographic studies in nonprimates: the ventral striatum [93]; the lateral segment of the globus pallidus [41]; the lateral preoptic region of the hypothalamus [91]; the central nucleus of the amydala [59]; the habenula [43]; the dorsal raphe nucleus [3]; and the nucleus tegmenti pedunculopontinus (Tgc) in the midbrain [26].

To date, however, we have found that large injections of HRP into the monkey's pars compacta, but not including the medially lying A10 area, do not produce any ventral striatal (or basalis nucleus), habenular or hypothalamic preoptic region retrograde cell labeling. In one experiment (SMT-2) in which the laterally lying peripeduncular nucleus was included in the injection area, labeled cells appeared in the hypothalamus, but they were restricted to the ventromedial and suprachiasmic nuclei, in accord with the autoradiographic observations of *Jones* et al. [51] on hypothalamic fiber connections with the peripeduncular nucleus in monkeys. Some weakly labeled cells appeared in the central nucleus of the amygdala in experiment SMT-2 but not in similar cat experiments. *Grofova* [33] described no amygdala or hypothalamic cell labeling after cat HRP nigral injections and concluded that the lateral GP cell labeling she found projected to the pars reticulata and not the pars compacta. *Hattori* et al. [41] ascribes to GPL connections with the compacta in the rat but *Faull and Mehler* [20] could not rule out subthalamic nucleus HRP contamination in comparable rat studies or in current nigral HRP experiments in cats and monkeys.

Large number of labeled cells appear in the dorsal raphe nucleus (dR) following nigral, striatal, or amygdala HRP injections indicating widespread multiple connections of individual cells in this raphe nucleus or some possible intranuclear dR topography that has yet to be determined. Both dR and the ventrally located, median raphe nuclei contain large numbers of serotonergic cells. The median raphe nucleus supplies serotonergic axons chiefly to limbic structures such as the septal nuclei and the hippocampus, and the dorsal raphe nucleus projects chiefly to basal gangliar structures such as the corpus striatum, nigra and amygdala [52, 78]. Stimulation of dR produces excitatory postsynaptic potentials (EPSPs) in caudate-putamen neurons followed by inhibitory (IPSP) potentials [115] . On the other hand, lesions of dR which lower 5-hydroxytryptamine (5-HT) in both the striatum [52] and the nigra [16], increase dopamine in these regions, suggesting a net inhibitory role for the dR serotonergic cell projections according to *Dray* [16].

Cells in the *pars reticulata* (SNr) are unpigmented in all species. In

Nissl sections, however, there are some pigmented cells that appear scattered in small islands or cellular isthmi connecting with the dorsally situated pars compacta in primate brains. The two layers appear somewhat more marbelized in primates than the apparent simple stratification of layers seen in most nonprimate nigras. The somata of the nonpigmented reticulata cells are generally smaller than cells in the pars compacta. There is also a *pars lateralis* subdivision of the reticulata that can be identified cytoarchitectonically in the rat, cat, and monkey. Massive afferent fiber connections converge on the SNr from the caudate and putamen in a medial to lateral topographical fashion [34, 117]. The existence of proposed cortical connections with either layer of the nigra has not been supported by ultrastructural studies [109], but complex intrinsic circuits have been suggested [24].

A brief sketch follows on the work in the past 20 years that lead to the discovery of the efferent fiber projection of SNr to the thalamus and tectum. Stereotactically placed lesions of the nigra in most cases produce heavy fiber degeneration that projects into the mesencephalic tegmentum and the tectum and often interrupts overlying lemniscal fibers ascending to the thalamus. Cortical ablation studies demonstrated that corticofugal fibers to these mesencephalic regions often coursed through the nigra. These observations dictated to us that both the apparent nigrotegmental and tectal connections were probably cortical in origin. However, utilizing angular stereotactic approaches to minimize lemniscal fiber damage contamination, nigral lesion experiments in the cat and monkey led us to propose that a *nigrothalamic* projection to the ipsilateral thalamus did indeed exist [9]. The chief terminus of the nigrothalamic projection in the monkey is the magnocellular part of the ventral anterior nucleus (VAmc) that appears to be cytologically homologus with the internal region of *Hassler's* [39] nucleus polaris and/or the nucleus ventro-oralis. HRP studies in nonprimates [20, 107] indicate that these projections originate chiefly from cells in the more lateral part of the SNr. These cells lie dorsal to those giving rise to the nigrotectal projection whose discovery is discussed next.

Nevertheless, before the advent of the new methods, we were still adamant in our belief that the tectal connections appearing in many of these selective nigral lesions were nigral in origin. Comparable silver studies in the rat [18] and monkey [5] confirmed the existence nigrothalamic projections and also disclosed tectal connections in many experiments. Like our group, the latter authors conservatively suspected concomitant

corticotectal fiber damage and denied the existence of a nigrotectal pathway. In 1975, however, *Graybiel and Sciascia* [30] applied the new autoradiographic method in which it is believed that the tritiated amino acid that is injected is taken up only by cell bodies in the region of the injection and *not* incorporated for transport by injured fibers. This study and a subsequent study by *Graybiel* [26] clearly demonstrated that nigral fiber projections to the superior colliculus terminated in irregular bands that run from rostral to caudal in the stratum intermedium of the tectum in the cat. *Jayaraman* et al. [48] have verified the banded nigrotectal connection autoradiographically in the monkey and *Graybiel* [26] has also found intense AChE-positive bands in the same stratum in the human superior colliculus that seem to correspond with the nigrotectal endings.

Our HRP studies of nigral projection patterns in the rat [20] confirmed that these nigrotectal-projecting cells in the reticulata lie chiefly in a deep layer ventral to those SNr cells giving rise to the nigrothalamic projection. In the rat these cells are concentrated medially in the rostral part of SNr and laterally in the caudal part. Essentially similar topological patterns seem to exist in the cat [26] and the monkey [46]. Recent neurophysiological and retrograde double marker experiments in the rat have provided evidence suggesting that there are some cells in the nigra with dual efferent projections, the branched axon of one SNr cell projecting to both the thalamus and the tectum [112].

The pars compacta of the *nucleus tegmenti pedunculopontinus* (Tgc) is the most caudal terminus of the pallidofugal outflow from the medial GP [92]. It is a reticular-like cell group located in the center of each half of the midbrain tegmentum at the level of the inferior colliculus. It is perforated by the ascending brachium conjunctivum, some Tgc cell clusters actually being intercalated in the brachium. There is no evidence, however, that the latter cerebellofugal fibers terminate, en passage, on Tgc cells. These cells are AChE-positive, not dopaminergic. Besides the massive MGP input to Tgc, descending afferent fiber connections from area 4 to Tgc have also been described.

The efferent projections of Tgc, on the other hand, are just beginning to be unraveled. Nauta-method studies of fiber degeneration issuing from lesions of Tgc have failed to reveal any unique diencephalic projections. These experiments (MT-111 and 137 [unpublished results]), however, suggested that Tgc axons ascend and project to the contralateral tectum via a long supraoptic loop [79]. New evidence revealed by autoradiographic fiber projections studies in the cat [26] suggests that Tgc axons pro-

ject to SN pars compacta, the subthalamic nucleus and also have reciprocal connections with the entopeduncular nucleus, the subprimate homologue of MGP. We have examined a large TAA injection of the Tgc region in a monkey from *Mantyh's* [71] thesis, comparable to *Graybiel's* cat experiment. The SN pars compacta in this case is selectively and heavily covered with radioactive grains and the underlying pars reticulata is absolutely clear. Coupled with the intense HRP cell labeling of Tgc cells observed in our SNc-injection experiments in the cat and monkey, it appears that the AChE-positive Tgc cells are a major source of afferent connections of the dopaminergic pars compacta of the substantia nigra.

In the course of our HRP study of the amygdala in the monkey [78], we had several injections that also involved the globus pallidus. These experiments, affecting MGP, labeled some cells in Tgc and, in certain cases, also produced copious anterograde pollidotegmental fiber terminals that outline Tgc, reminiscent of terminations previously seen in fiber degeneration studies [92]. *DeVito* et al. [14] have also found some Tgc cells labeled after HRP injections into MGP in monkeys.

Following *Olszewski and Bacter's* [95] interpretation, we labeled the randomly distributed pigmented cells in the ventral lateral tegmentum dorsal to the medial lemniscus as belonging to the 'pars dissipatus' of the nucleus tegmenti pedunculopontinus (Tgd). It appears that we [92] inadvertently identified terminals of striatonigral-like fibers in the so-called pars dissipatus in our MGP lesions and misinterpreted them as pallidal projections to what appeared to be two parts of the same tegmental nucleus (e.g. Tgd and Tgc). Fluorescence histochemical studies, however, have identified dopaminergic cells in this 'Tgd' region in nonprimates [11] and primates [25] designated A8. These A8 cells (sometimes called the retrorubral nucleus), like the A9 pars compacta of SN, are consistently labeled with HRP injections into caudoputamen in the rat and cat indicating that they, like SNc cells, also project to the striatum. Labeled A8-like cells also appear in monkeys in some of our more restricted HRP striatal injections suggesting that the A8 cells probably have a specific topographic distribution to some region in the functional mosaic of the striatum that is yet to be isolated in the primate brain. On the other hand, these cells appear to receive descending striatal fiber connections which normally converge only on cells of the nondopaminergic pars reticulata, consensus being that pars compacta does *not* receive striatofugal connections per se and that the chief sources of afferents to the compacta is still *unknown*

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The Claustrum

Following HRP injections into various areas of the cerebral cortex in cats and baboons, *Riche and Lanoir* [106] found labeled cells widely dispersed in the claustrum. They found HRP-positive cells in the caudal part of the claustrum subsequent to injections of the visual cortex and labeled cells in rostral regions following motor or sensory cortex injections. Based on their observations that injections of area 8 (frontal eye fields) in the baboon or the gyrus proreus in cats resulted in the most extensive cell labeling throughout the rostral two-thirds of the claustrum, they suggested that the claustrum might be concerned with the integration of visually directed movements.

Macchi et al. [70] have confirmed and extended evidence that there are widespread clausal connections to all of the major cerebral cortical areas. Following HRP injections into various parts of the visual, auditory, and first and second somatosensory cortices in the cat, they found labeled cells distributed in anteroposterior and dorsoventral topographical arrangements. There is some degree of overlap in most of these topographical 'pools' of claustral cells projecting to various cortices. *Macchi* et al. [70] point out that these claustral projections terminate in layer I, as 'nonspecific' thalamocortical fibers were classically conceived to terminate, but they also have extensive layer IV terminations where 'specific' thalamocortical connections were traditionally believed to terminate. They note, however, that these 'specific' thalamic nuclear projections have now been shown by autoradiography also to have superficial layer I cortical connections, a fact that partially disrupts several old theories based upon specific versus nonspecific cortical afferent input. *Afferent connections* of the claustrum appear to originate chiefly in the cerebral cortex [53, 60].

The Amygdala

The connections of the enigmatic amygdala have finally begun to be unraveled. Afferent connections originating in secondary olfactory areas, the orbitofrontal cortex and from wide areas of the temporal lobe have recently been clarified [113]. Some reciprocal hypothalamic connections

that were thought to exist have been verified and several new interconnections have been suggested [59]. Up until 1978, however, only a limited projection to the amygdala from the magnocellular part of the medial dorsal nucleus of the dorsal thalamus was thought to exist.

Silver stains were apparently refractory in demonstrating most of the subcortical afferent and efferent connections of the amygdala now being discovered with the new retro-, and anterograde axon transport methods. For example, stereotactic injections of horseradish perioxidase (HRP) into the amygdaloid complex in monkeys [78] retrogradely labels cells throughout the ipsilateral half of the paraventricular nucleus of the thalamus that completely surrounds the dorsomedial edge of the dorsal thalamus just beneath the choroid plexus that forms the roof of the third ventricle. HRP-positive cells are also found in some of the adjoining *midline* intralaminar nuclei that occupy the *massa intermedia* in primates. In the absence of a *massa* spanning the third ventricle, such as is found in many humans brains, these nuclei form bilateral, concentric masses lining the ventricle on the medial surfaces of each thalamus. A sheet of amygdalopetal HRP-positive cells constituting the nucleus *sub*parafascicularis stretches from the edge of third ventricle caudolaterally *beneath* the parafascicular nucleus and the ventral posterior nuclear complex almost to the medial part of the medial geniculate body. At this level the prethalamic lemniscal systems separates the tegmental-like subparafascicularis nucleus from another large collection of cells that project to several nuclei of the amygdala; the peripeduncular nucleus of *Jacobson* [47] which was first recognized in man [51].

Recent studies have also shown that besides the ventromedial nucleus of the hypothalamus, that has previously known reciprocal connections with the amygdala, there are a number of other nuclei in the hypothalamus such as the supramammillary nucleus and the lateral hypothalamic nucleus which also have cells projecting to the amygdala. There are amygdalopetal projections from various ventral tegmental, paranigral nuclei constituting dopaminergic cell groups A10 and A8 of *Dahlstrom and Fuxe* [11] that also connect with the accumbens nucleus or fundus striati (of man) as we have previously noted. Raphe nuclei in the midbrain containing serotonergic cells, especially the dorsal raphe nucleus, also project to both the amygdala and widely throughout the corpus striatum, as do adrenergic cells of the locus ceruleus. The most caudally located cell groups projecting to the amygdala in the monkey are the parabrachial nuclei adjacent to the locus, chiefly the lateral parabrachial nucleus [78].

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HRP studies by *Hopkins* [44] first indicated that there were long *efferent* projections from the amygdaloid complex to brainstem nuclei that originated chiefly from the central nucleus and from the magnocellular part of the basal nucleus. Following ^{3}H-leucine injections into the central nucleus in the cat, *Hopkins and Holstege* [45] subsequently traced fiber projections autoradiographically into the lateral hypothalamus through the mesencephalic tegmentum, where they gave off collaterals to the periaqueductal gray, and then continued into the dorsolateral pontine tegmental region where they terminated heavily on the parabrachial nuclei. The remaining fibers of this extensive amygdalofugal fiber system traverse the parvocellular reticular region from the level of the pons caudad to the level of the obex, distributing dense terminal endings to parts of the solitary nucleus and to the dorsal motor nucleus of the vagus.

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