THE DISTRIBUTION OF FIBERS FROM AMYGDALA, THALAMUS AND CORTEX WITHIN THE STRIATUM OF THE CAT

by

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Abstract

The mammalian striatum (caudate nucleus and putamen) is composed of two mingled tissue compartments, designated striosomes and matrix, that are distinguished according to neurochemical content. It is known that the distributions of striatal projection cells and at least some afferent fiber-systems reflect this chemoarchitecture. In this thesis I present a detailed account in the cat of forebrain afferent connections that observe the histocompartmental structure of the striatum and explore the implications for striatal processing of the differential input to striosomes and matrix.

Projections to the striatum and ventral striatum from amygdala, thalamus and cortex were labelled by anterograde axonal transport of a horseradish peroxidase-wheat germ agglutinin conjugate, ^{35}S-methionine or a mixture of ^{3}H-leucine and ^{3}H-proline. The arrangement of the striosomes, demonstrated as enzyme-poor zones in tissue sections stained for acetylcholinesterase activity, was then compared by serial-section analysis with the patternings of the experimentally labelled fibers.

Deposits placed in thalamus, when analyzed according to the compartmental target of the labelled fibers, establish medial and lateral thalamostriatal projection-systems. The lateral system, which embraces the centromedian-parafascicular nuclear complex, the anterior intralaminar nuclei, the rostral ventral tier nuclei and parts of the posterior lateral nuclear complex, predominantly innervates matrix tissue; the medial system, which includes the paraventricular and rhomboid nuclei of the midline system, primarily projects to striosomes.

Deposits of anterograde tracer centered in the basolateral nucleus of the amygdala produce labelling of the ventral striatum and of striosomes in ventral and medial

caudate nucleus. Labelling in ventral matrix tissue, where present, appears due to injection-site encroachment on neighboring amygdalar nuclei. A close connectional relationship among ventral striosomes, the ventral striatum and the basolateral nucleus is confirmed by a finding of heavy labelling of the basolateral nucleus and of ventral striatum in all of the medial thalamic cases. The medial thalamostriatal system, though, is markedly distinguished from the fiber-connections of the basolateral nucleus in innervating striosomes throughout the striatum, including dorsal (parieto-recipient) and dorsolateral (sensorimotor-recipient) districts from which amygdalar projections are excluded.

Deposits placed in an expanse of tissue extending from prefrontal cortex across the insula to rostral temporal cortex elicit labelling of striosomes. With the exception of the injection sites situated in ventromedial prefrontal and rostral temporal cortices, which evoke labelling of striosomes in ventral caudate nucleus and of ventral striatum, the structure of the projections produced by these deposits is quite elaborate, with fibers 'filling' striosomes dorsally in their striatal field of termination while ventrally 'avoiding' striosomes and instead innervating matrix tissue. For example, deposits in dorsomedial prefrontal cortex elicit labelling of striosomes in dorsal caudate nucleus and of matrix in central and ventral caudate nucleus; and injections into the insula produce labelled striosomes throughout all of the caudate nucleus except at its base. There the insular fibers innervate matrix tissue. This 'dorsal fill/ventral avoid' pattern suggests that the linkage by shared afferentation of ventral striosomes and ventral striatum can be generalized to any collection of striosomes and the matrix tissue subjacent to them. Projections directed exclusively to matrix tissue issue from anterior parietal cortex (to dorsolateral caudate nucleus), from posterior association cortex (to dorsocentral caudate nucleus), and from cingulate cortex (to medial caudate nucleus).

There can be no simple account of the difference between inputs to striosomes and matrix if single cortical areas produce a double pattern of innervation. However, a more formal description is possible: cortical regions that overlap in their projections to striatum can be ordered according to the dorsoventral level at which their fibers favor matrical over striosomal tissue. For the middle part of the striatum this ordering is <parietal, dorsomedial frontal, ventrolateral frontal, insula, rostral temporal> cortex where the leftmost, or 'lowest', structures project to dorsal matrix and the rightmost, or 'highest', elements project, as the basolateral nucleus of the amygdala does, to ventral striosomes and ventral striatum. The relationship of the cortical input of any striosome to that of the adjoining matrix tissue can then be described explicitly. The striosomal input arises from cortex that is higher in the ordering.

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Chapter 1

Introduction

The concept of an extrapyramidal motor system was secured by the independent observations of C. Vogt (1911) and S.A.K. Wilson (1912) that a clinical syndrome of involuntary movements could result from pathology restricted to the corpus striatum. Wilson's evidence issued from study of a familial disease of progressive lenticular degeneration that produced involuntary movements, most notably a bilateral tremor of the extremities, dysarthria and a marked rigidity of the musculature (Wilson's disease). His interest in the disease was not limited to its witness to a motoric function for the striatal system (the lenticular nucleus consists of the putamen and the globus pallidus). He recognized the similarity of its symptomatology to that of Parkinson's disease and suggested, as we now know correctly, that this far more common disorder might too be of an extrapyramidal system. Vogt, for her argument that the striatal system should be viewed as a motor center independent of the pyramidal system, documented the presence of athetoid movements (double athetosis) in patients that on *post-mortem* examination presented bilateral, marbled atrophy of the corpus striatum (status marmoratus). Her recognition that involuntary movements produced by destruction in the corpus striatum are not restricted to tremor, but include choreic and athetoid symptoms, presaged the inclusion of a number of disorders, notably Huntington's disease and hemiballism, among those of the extrapyramidal system. Seventy-five years later their clinico-pathological determination that damage to the striatal system can produce involuntary movements remains sound. Moreover, it still provides the greatest insight, dark though it may be, into the functions of this

area of brain. Their conclusion that the corpus striatum is part of an extrapyramidal motor system also appears in essence correct; it was, however, based on anatomy and physiology that is now known to be mostly wrong.

For Vogt (1911) and Wilson (1914), the extrapyramidal system consisted of the striatum (caudate nucleus and putamen) and the globus pallidus (together these structures constitute the corpus striatum), the subthalamic nucleus, the substantia nigra and the red nucleus. Two points in their understanding of the anatomy of this system were crucial to their belief that its access to the spinal motor apparatus was extrapyramidal. The first was that its circuitry was independent of the cerebral cortex and the second was that the efferent connections of the striatal system were carried over the rubrospinal pathway. Their analysis, then, was that the striatal system, by clinical evidence, participated in the motor system, that in attaining the red nucleus it had a non-pyramidal access to the spinal cord and that in maintaining no connections with the cortex it was be guaranteed to have no connections with the pyramidal system. We know now that the striatal system is strongly affiliated with the cerebral cortex: the striatum receives connections from nearly all areas of the cortex, including all those regions that issue pyramidal tract fibers, and the major output of the corpus striatum is a trans-thalamic circuit to areas of frontal cortex, some of which participate in the formation of the pyramidal tract. Furthermore, there is no credible evidence that the corpus striatum or any of its immediate affiliates are afferent to the rubrospinal tract. Thus, the anatomy deployed by Vogt and Wilson to situate the corpus striatum in an extrapyramidal motor system was not sound. To investigate the correctness of their conclusion, though, it seems reasonable to pursue their analysis: given a role for the corpus striatum in the motor system, what descending motor tracts does it have access to?

The pyramidal tract arises in the cortex, passes through the medullary

pyramids and distributes to the spinal cord. Its origin is not restricted to one cortical area, such as motor cortex, nor are the motor effects of destroying any part of cortex limited to pyramidal mechanisms. However, a circuitry must reach the cortex if it is to influence the pyramidal tract. Extrapyramidal fiber-systems are understood to be the remaining, obviously quite numerous pathways by which the brain gains control over the spinal motor system. These include descending tracts originating in the tectum, pontine and medullary reticular formation and the red nucleus, and, by extension, those parts of brain that provide input to these tracts. This view of extrapyramidal circuitry would straightforwardly include cerebellum, in part because of its strong afferentation of the magnocellular red nucleus, and motor and premotor cortices, including areas that also give rise to pyramidal fibers.

From the anatomical data reviewed so far, the extrapyramidal system of Vogt and Wilson, exclusive of the red nucleus, does not warrant easy inclusion among extrapyramidal fiber-structures as just outlined. This is particularly ironic as many modern authors, following Wilson, would reserve the term extrapyramidal system for precisely these nuclei and exclude even the cerebellar system from this designation. Given this confusion, it seems safer to use the older term basal ganglia, which in current practice *is* restricted to the corpus striatum, subthalamic nucleus and substantia nigra, and to take the question of basal ganglia involvement in extrapyramidal mechanisms as one open to investigation.

A sketch of basal ganglia anatomy

The connections among the nuclei of basal ganglia, though often reciprocal, are when analyzed by relative volume strongly polarized. The striatum, by far the largest of the nuclei, receives the bulk of its innervation from outside the basal ganglia, mainly from thalamus and cortex. Its efferent projections are almost exclusively within the basal ganglia, to the globus pallidus (pallidum) and the pars

reticulata of substantia nigra. By contrast, the afferent connections to the pallidum and nigra arise largely from within the circuitry of the basal ganglia, and mainly from the striatum, and the chief efferent connections of the pars reticulata of the nigra and of the internal segment of the pallidum are with structures outside the basal ganglia, most notably thalamus, tectum and parts of the reticular formation (for a detailed review of the literature drawn upon here, see Graybiel and Ragsdale, 1979).

Arranged along this principal pathway through the basal ganglia are a number of subordinate circuits. Two of these are of major clinical importance and account for the anatomical relations of the remaining principal nuclei of the basal ganglia: the subthalamic nucleus and the pars compacta of the substantia nigra. The subthalamic nucleus is strategically positioned to modulate the targets of striatal outflow. Its dominant afferent connection originates as the main projection of the external segment of the pallidum. Its efferent connections return this projection and in addition reach the internal segment of the globus pallidus and the pars reticulata of the substantia nigra. Destruction of the subthalamic nucleus is known to have a devastating effect on the motor system, producing a hemi-chorea of great amplitude and violence (hemi-ballism).

The pars compacta of the substantia nigra gives rise to the celebrated dopamine-containing nigrostriatal pathway. Though the contribution of this input to striatal processing remains obscure, its integrity is vital. It is these neurons that die in Parkinson's disease, producing bradykinesia, rigidity and tremor. The afferent circuitry of the cells has proved technically to be difficult to study, but it now seems clear that a large part of their input arises within the basal ganglia. The dendrites of many compacta cells extend into the adjoining pars reticulata and so are positioned to accept both local and striatal connections. The cell bodies

themselves may receive direct input from parts of the striatal complex, and possibly from pallidum as well. In addition they receive a marked projection from the tegmental pedunculopontine nucleus of the pontomesencephalic reticular formation. This structure is known to be well-integrated into basal ganglia circuitry as its major afferent nuclei include the pallidum and the nigra.

The dopamine cells of the midbrain are not restricted to the pars compacta of the nigra (designated monoamine cell-group A9 in the typology of Dahlstrom and Fuxe (1964)). There are also major aggregations in the ventral tegmental area (cell-group A10) and in the ventral mesencephalon caudal to the red nucleus and dorsal to the nigra (cell-group A8). Because they contain dopamine, adjoin the A9 cell-group and also project to the striatum, the A8 and A9 neurons are often considered outlying nigral cell-groups. It is not clear for these neurons that the majority of their afferent fibers originates among basal ganglia nuclei. In particular, the A8 cell-group appears removed from this circuitry and should possibly be considered an additional extra-basal ganglia input to the striatum.

This brief sketch is in no way fair to the considerable complexity of the anatomy of the basal ganglia. The afferent connections of the striatum, for example, include significant input from the basolateral amygdala and the nucleus of the dorsal raphe. Moreover, the distribution of extrinsic input to the basal ganglia is by no means restricted to the striatum- the dorsal raphe reaches most of its nuclei and sparse input from thalamus or cortex has been documented for the globus pallidus, substantia nigra and subthalamic nucleus. There are in addition important nuclei connectionally yoked to the basal ganglia, such as the pedunculopontine nucleus (described above) and the posterior intralaminar nuclei of the thalamus. The purpose of this review is to suggest that, in spite of the intricate interconnections among basal ganglia structures, the rough circuitry is

straightforward and that, at least initially, an inquiry into the processing roles of the basal ganglia might profitably restrict itself to a study of its main inputs and outputs, which are the afferent connections of the striatum and the efferent targets of the pallidum and nigra.

The 'escape routes' of basal ganglia circuitry, then, are those of pallidum and nigra and, as noted above, include the thalamus, the tectum and the pedunculopontine nucleus in the reticular formation. In judging differential access to motor system mechanisms, the trans-thalamic route is most problematic because the pyramidal and extrapyramidal systems are not clearly segregated at the level of cortex. However, some tendencies are evident. The basal ganglia targets in the ventral tier thalamus- parts of the ventral anterior (VA) and ventral lateral (VL) and, in subprimates, ventral medial (VM) nuclei- together reach much of the frontal cortex. There is, however, no good evidence in the monkey, and no compelling evidence in the cat, that these nuclei project to motor cortex, to parietal cortex or even to all premotor fields. These projections are then excluded from most of the areas of cortex that give rise to pyramidal tract fibers. The supplementary motor area (SMA) of the primate is the only region of cortex that clearly both receives basal ganglia-recipient ventral thalamic fibers (from the oral part of the ventral lateral nucleus- VLo) and projects to the spinal cord (Schell and Strick, 1984; Catsman-Berrevoets and Kuypers, 1976). However, analysis of anterograde and retrograde tracing studies indicates that the main projection of the SMA beyond the midbrain is *not* to the spinal cord, but rather to the medial reticular formation of the hindbrain- the source of a major extrapyramidal pathway, the reticulospinal tract (Kuypers and Lawrence, 1967; Kalil, 1978; Catsman-Berrevoets and Kuypers, 1976). An even more pronounced extrapyramidal circuitry holds for the opercular cortex adjoining the SMA and

lying medial to the superior limb of the arcuate sulcus- this region is a major target of the VA-VL complex, does not participate appreciably in the formation of the pyramidal tract and projects heavily to the lower brainstem (Kievit and Kuypers, 1977; Catsman-Berrevoets and Kuypers, 1976). The status of basal ganglia outflow beyond area 6, to parts of prefrontal cortex, is less certain. It is clear that pyramidal circuitry is not easily reached from these cortical regions and that the tectum *inter alia* is. This could, however, be more a reflection of a lack of involvement in the skeletal motor system than of a preferential affiliation for extrapyramidal circuitry (see below).

Basal ganglia outflow that bypasses the thalamus clearly does not have access to the pyramidal system, but is apparently positioned to participate in non-pyramidal pathways to the cord. This arrangement is clearest for the superior colliculus, which is a major target of descending nigral efferent fibers and gives rise to axons that travel in the predorsal bundle to medial reticular formation and cervical levels of the spinal cord. Anatomical studies suggest that an intra-collicular linkage of these systems may be quite immediate: the principal zone of termination of the nigrotectal projection is the intermediate gray, a layer of the colliculus in which cells projecting to the spinal cord are known to reside (Graybiel, 1978; Jayaraman et al., 1977; Kuypers and Maisky, 1975; Castiglioni et al., 1978). This relationship has been recently examined in detail by May and Hall (1984) in the squirrel, an animal with a highly organized tectum; they found that the nigrotectal pathway ends within the precise sublayer of origin of the predorsal bundle. Interestingly, recent work in the cat suggests that this nigro-recipient part of the intermediate gray may serve as a major site of convergence of basal ganglia output as it also receives direct connections from parts of frontal cortex linked trans-thalamically with the basal ganglia (Illing and Graybiel, 1985).

The major reticular formation terminations of the nigra and pallidum are in the pedunculopontine nucleus of the pontomesencephalic tegmentum. Though the main efferent connections of this nucleus are ascending, return projections to the basal ganglia, it does engage in descending projections to parts of the pontomedullary reticular formation that give rise to the reticulospinal systems (Moon Edley and Graybiel, 1983). Physiological evidence supports the view that these reticulo-reticular connections lead to spinal motor mechanisms: the pedunculopontine nucleus, though apparently distinct and separate from the 'mesencephalic locomotor region' as classically defined (Moon Edley and Graybiel, 1983), does, when stimulated, inaugurate patterned treadmill walking in cats with transections of rostral brainstem (Garcia-Rill, 1986).

Some findings on the physiology of motor pathways efferent to the basal ganglia

From the modern anatomy reviewed, it is clear that basal ganglia access to the motor system can operate over extrapyramidal tracts. Moreover, it appears that, even at the cortical level, extrapyramidal mechanisms may be favored. For Vogt and Wilson, though, the conclusion that lesions of the corpus striatum affected the extrapyramidal motor system depended not only on available anatomy, but also on contemporary understanding of the physiology of the pyramidal system. This understanding held that pyramidal lesions disrupted normal reflexes and produced spasticity and paralysis. It is now known that pyramidectomy does not produce spasticity and that, following a period of paresis, most all motor performance recovers. In their examination of the motor consequences of bilateral section of the medullary pyramids, Lawrence and Kuypers (1968a) concluded that, although it did confer speed and agility to motor performance, the corticospinal pathway was *necessary* only for highly fractionated movements, such as individual movements of the fingers. As the 'negative signs' of corpus striatum destruction

clearly extend beyond these deficits, a conclusion of extrapyramidal involvement in striatal dysfunction appears warranted. Similarly, a motor pathway such as the pyramidal tract would not be the expected mediator of many of the 'positive signs' of striatal system damage, which include tremor, rigidity and chorea.

In analyzing the logic of the physiology of these 'positive signs', though, one must be cautious. Since basal ganglia lesions do 'release' these movements, they clearly are under basal ganglia control; yet as Hughlings Jackson has argued, destructive lesions can not *cause* these involuntary movements. Wilson, for one, held that what were released were trans-cortical and cerebello-cortical 'reflexes' (Wilson, 1912; Wilson, 1925). Since his time we have learned much on this problem from neurosurgical approaches to the treatment of involuntary movement disorders. These clearly indicate that while negative signs such as the bradykinesia of Parkinson's disease can not be significantly ameliorated by surgical intervention, many of the positive symptoms can be reduced or abolished by lesions placed efferent to the pathology. For example, lesions of the internal segment of the pallidum and of pallido-recipient ventral thalamus can ameliorate or eliminate the rigidity of Parkinson's disease and the ballism produced by subthalamic nucleus damage (Hassler et al., 1979; Martin and McCaul, 1959). Lesions of basal ganglia-recipient ventral thalamus are also effective in treating athetotic disorders and some dystonias as well as the L-DOPA-induced dyskinesia of Parkinson's disease (Narabayashi and Kubota, 1966; Narabayashi et al., 1984). These findings strongly suggest that, for many symptoms, what is released lies within basal ganglia circuitry, and probably involves disordered processing that exits by way of the internal pallidal segment. Only the tremor of Parkinson's disease is clearly excepted from this conclusion. The target of choice to relieve this positive symptom is caudal to pallidorecipient ventral thalamus, in a district where cerebellar information is relayed to motor cortex.

This evidence that many of the movements released by striatal system damage do flow from basal ganglia structures suggests that the circuitry transmitting the 'positive signs' probably are also responsible for normal striatal action. It validates as an approach to the identification of descending motor pathways that mediate basal ganglia function, the study of the consequences of lesions placed secondary to basal ganglia pathology. To date, this approach has only been tried in an experimental setting by Mettler and Carpenter and colleagues. In large part due to their work it has become popular to view the lateral corticospinal tract as the target of the striatal extrapyramidal system (Carpenter, 1961; Hassler et al., 1979).

Whittier and Mettler (1949) and Carpenter et al. (1950) established that unilateral destruction of the subthalamic nucleus can produce a hyperkinesia similar to the hemiballism of human pathology. They proceeded to show that the disordered movement could be blocked by lesions of the pallidum or of the ventrolateral thalamus, indicating that a transcortical trajectory was likely[1]. They then turned to transections of the spinal columns and established that interruption of the ventral funiculus and the ventral half of the lateral funiculus, though ameliorating, did not stop the movements while destruction of the dorsal half of the lateral funiculus did (Carpenter et al., 1960). This relief persisted past a post-surgical interlude of paresis. In their view the relevant interrupted pathways were the rubrospinal and lateral corticospinal tracts, and as they had previously found

[1]Carpenter and Mettler (1951) did study the effects of lesions of area 6 (but *not* including the SMA) on the hyperkinesia. They found abolition of the chorea only when the wound extended into area 4; in these animals a hemiparesis was also produced. Their interpretation was that motor cortex mediated the ballism. This could well be (note that motor cortex participation would not be guarantee, or even strongly indicate, pyramidal tract involvement), but strictly speaking, tissue destruction that blocks involuntary movements by induction of paresis are utterly useless in distinguishing among descending motor pathways (cf. Bucy and Buchanan, 1932).

that red nucleus lesions do not abolish subthalamic hyperkinesia (Carpenter and Brittin, 1958), they concluded that the corticospinal tract is the mediator of the motor disturbance.

For a critical inspection of these experiments, we must first review the full analysis of Lawrence and Kuypers concerning the functional organization of descending motor pathways. These workers examined the supplemental effects, following pyramidectomy, of lesions of the descending tracts originating in brainstem (Lawrence and Kuypers, 1968b). They distinguished a lateral and a ventromedial system, where the position term refers to the course taken by the constituent fibers in lower brainstem and spinal cord. The fibers of the ventromedial system originate in the medial pontine and medullary reticular formation and in the vestibular nuclei and the interstitial nucleus of Cajal. The tectospinal pathway also travels with this system. According to Lawrence and Kuypers (1968b), these "ventromedial brainstem pathways ... function as the basic system by which the brain exerts control over movements... [They are] especially concerned with maintenance of erect posture, integrated movements of body and limbs and with directing the course of progression." The lateral system is mostly accounted for by the rubrospinal tract and appears responsible for independent movement of the distal extremity and the hand.

What is immediately striking in this analysis is the likeness of the kinds of motor functions mediated by the ventromedial system and the kinds of dysfunctions one sees in striatal system disorders, such as bradykinesia, postural disorders including dystonias and some forms of choreo-athetosis. The lateral system also appears a good candidate for some categories of movement, in particular that of hemiballism. This is consistent with the findings of Carpenter et al. (1960) that dorsolateral funicular lesions relieve the subthalamic dyskinesia, but

not with their interpretation that the crucial lesion was of the corticospinal pathway (recall that for Lawrence and Kuypers the only individuated task of the corticospinal system was highly fractionated movements, such as of the fingers). A resolution of this discordance may lie in recent studies of bulbospinal circuitry. Both anatomical and physiological evidence indicate that reticulospinal pathways are not, as contemporary anatomy led Carpenter to believe, restricted to anterior routes, but extend to lateral and dorsolateral ones as well (Engberg et al., 1968; Nyberg-Hansen, 1965; Burke et al., 1972). To take two examples, there is now good anterograde evidence that the spinal projections from the magnocellular reticular nucleus of the rostral medulla travel in the dorsolateral fasciculus (Basbaum et al., 1978), and there is compelling retrograde evidence for a major crossed pontospinal tract which descends with the rubrospinal pathway (Kuypers and Maisky, 1975; Kuypers, 1981). The magnocellular reticular nucleus is plainly positioned to receive afferent input both from the tegmental pedunculopontine nucleus and from cortical areas, such as the SMA, in receipt of basal ganglia output (Moon Edley and Graybiel, 1983; Kalil, 1978). While the afferentation of the crossed pontospinal pathway is not clear, it appears situated to receive input from the intermediate gray of the superior colliculus as well as from the pedunculopontine nucleus and premotor cortex (Martin et al., 1979; Moon Edley and Graybiel, 1983; Kalil, 1978). To decide this question, the experiments on ballism must be repeated with *pyramidal* tract interruption. Although we can not exclude corticospinal tract mediation of some basal ganglia functioning, the conclusions of Carpenter et al. (1960) are no longer warranted. It, in fact, seems most likely that their dorsolateral funicular lesions disrupted the lateral brainstem system of Lawrence and Kuypers.

The corticospinal tract has also been seen as responsible for the delivery of

the tremor of Parkinson's disease. The evidence for this is as before: dorsolateral, but not ventral, funicular lesions relieve the symptoms (Putnam, 1940). A determination that the pyramidal tract is involved is therefore open to the same anatomical criticism just offered. The analysis of Kuypers and Lawrence, however, does not particularly suggest a motor pathway that might mediate tremor and it may well be that Parkinsonian tremor is carried over the pyramidal tract. Note that, unlike conclusions following from the physiology of other involuntary movements, this one would not be informative about whether basal ganglia output travels over the pyramidal tract because tremor appears to be a release by basal ganglia of a cerebellar mechanism (see above).

Finally, I turn to the ventromedial system. As noted earlier, its physiological character appears to make it a good candidate for mediating many of the striatal involuntary movements disorders. This candidacy has support not only from anatomical studies (the ventromedial system includes most of the reticulospinal pathways and the tectospinal tract), but also from the literature on neurosurgical interventions: anterior cordotomies provide impressive relief from athetosis and dystonia (Putnam, 1933; Putnam, 1938).

This review of the anatomy and pathophysiology of the striatal system's access to descending motor pathways supports the extrapyramidal characterization of Vogt and Wilson. Although pyramidal tract involvement can not be excluded, the data reviewed indicate at the very least an extrapyramidal sovereignty. Consider, for example, the transthalamic destination of basal ganglia output in comparison with that of its partner in extrapyramidal circuitry, the cerebellum. Almost all of the cortical targets of the cerebellum are significant sources of corticospinal projections, while the basal ganglia strictly prefers areas that give rise to corticobulbar projections to such premotor cell groups as the tectum and the

medial reticular formation of the lower brainstem. More generally, what is remarkable about the efferent connections of the basal ganglia is the breadth of their access to descending motor pathways[2]. It might be argued that, though it is true that basal ganglia eventually reaches premotor neurons, it does so only after many synapses; to say that it is part of the motor system is, at best, misleading. But such an argument confuses *interrupted* circuits with indirect or weak ones. The outflow from the striatum, when examined in terms of the principal destination of each successive target, travels clearly and directly, and with many stops, into premotor circuitry.

The involvement by the striatal system in motor function is, moreover, not restricted to control of the skeletal musculature; it includes oculomotor function as well. From the anatomy, it is known that basal ganglia outflow reaches the intermediate gray of the superior colliculus and frontal cortex dorsal to the arcuate sulcus (and possibly even the frontal eye fields (Carpenter et al., 1976; Kunzle and Akert, 1977)), all areas which on physiological grounds clearly participate in the control of eye movements (Wurtz and Albano, 1980; Schlag and Schlag-Rey, 1987), and studies of the circuitry of basal ganglia-affiliated medial reticular formation establish that it projects directly to oculomotor nuclei (Graybiel, 1977b). Strictly on anatomical grounds, though, it is difficult to demonstrate a basal ganglia input to pathways that control the eyes that is separate from that that controls the head as the circuitries of these systems are tightly joined: except for a rostral part of the oral pontine reticular nucleus, all of the medial reticular formation of the pons and rostral medulla issue descending fibers that reach at least as far as the cervical

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[2]The range, in fact, appears to be much greater than that outlined here. To consider one particularly prominent example, pallidal efferents almost certainly terminate in the (prerubral) nucleus campi Foreli, a source of projections to the oculomotor apparatus and to the cervical cord (Nauta and Mehler, 1966; Nauta, 1979; Graybiel, 1977a; Huerta and Harting, 1982)

cord (Kuypers and Maisky, 1975; Huerta and Harting, 1982). Physiological data are, therefore, crucial here. First, frank stimulation of the caudate nucleus produces not only turning of the head but also shifts in gaze (Jung and Hassler, 1960; Laursen, 1963). Second, single-unit data collected in caudate nucleus and substantia nigra are argue for a participation in the control of eye movements (Hikosaka and Wurtz, 1983c; Hikosaka and Sakamoto, 1986). Third, physiological and pharmacological studies of superior colliculus point to involvement of the nigrotectal pathway in the generation of goal-directed eye movements (Hikosaka and Wurtz, 1983d; Hikosaka and Wurtz, 1985a; Hikosaka and Wurtz, 1985b). Finally, there is compelling clinical evidence for oculomotor disturbances in basal ganglia disorders (Corin et al., 1972; DeJong and Melvill Jones, 1971; Brooks et al., 1986).

* * *

Somehow, this apparent control over the *whole*[3] motor system has never seemed enough of a job for the basal ganglia, at least to many of its students. So other roles have been sought, and found (Teuber, 1976), and almost all of these added roles are what would now be described as cognitive in nature (Oberg and Divac, 1979).

There are two central lines of evidence adduced for a striatal role in cognitive functioning: the properties of single-unit responses recorded in basal ganglia and

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[3]In fact, the anatomical evidence for basal ganglia control over cranial branchiomeric and hypoglossal motor nuclei is not strong. The trans-cortical pathways that control these nuclei are not well understood and reticular formation fibers that reach these nuclei do not, with the exception of those to a portion of the facial nucleus, issue from the medial tegmental fields (Holstege et al., 1977). There is little doubt, though, about striatal system control here. The correlative evidence of single-unit physiology indicates 'face' representation throughout the basal ganglia (Liles, 1979; Crutcher and DeLong, 1984; DeLong et al., 1985), and there is extensive clinical testimony for bucco-lingual dysfunction in basal ganglia disease and in L-DOPA- and neuroleptic-induced kinesias (Agid et al., 1979; Yahr, 1976).

the behavioral consequences of damage caused by experimental destruction or disease. Notably for the concerns of this thesis, both interpretation and critical evaluation of these experiments depends crucially on arguments grounded in anatomy. For some investigators, in fact, basal ganglia anatomy by itself, that is, without recourse to data on the physiology of striatal function, has been taken as a line of evidence for 'cognitive processing' in basal ganglia (Alexander et al., 1986). A rough version of this approach is: the striatum consists of the caudate nucleus and the putamen, these structures are not connected so the functional role of each structure is therefore constrained by the range of extrastriatal inputs it receives, the putamen (in the primate) receives projections from the motor cortex and the caudate nucleus does not so striatal motor functioning must be restricted to the putamen and the caudate nucleus must be doing something else. There are many criticisms one can make of this argument, one of the most obvious being that at least a respectable portion of the caudate nucleus must be devoted to control of eye movements (Kunzle and Akert, 1977; Hikosaka and Sakamoto, 1986). I will, though, defer for the moment a full discussion of this argument; I only sketch it in brief form now as it informs review of the physiological and behavioral data.

A short review of some evidence for a 'cognitive' role for striatum

It is well-established that neurons in the putamen and pallidum of the monkey show phasic changes in their rate of firing in association with trained movements of the limb (DeLong, 1971; Crutcher and DeLong, 1984; Liles, 1985; Kimura, 1986; Alexander, 1987; Mink and Thach, 1987) and, recently, Hikosaka and Wurtz have demonstrated similar associations between triggered saccadic eye movements and discharge rates in the caudate nucleus and substantia nigra (Hikosaka and Wurtz, 1983a; Hikosaka and Sakamoto, 1986). Motor acts are not, however, the only determinants of basal ganglia neural activity. Neurons in the

striatum, pallidum and nigra respond to visual and auditory as well as sensory stimulation (Krauthamer, 1979; Hikosaka and Wurtz, 1983a; Hikosaka and Wurtz, 1983b; Strecker et al., 1985). Moreover, the conditions under which sensory responses are elicited can be quite complex. For example, Hikosaka and Wurtz (1983c) have described units in the pars reticulata of the substantia nigra that exhibit "memory-contingent visual responses". These neurons will fire in response to a spot of light shown briefly if the animal is to saccade to the location of that spot after a delay, but *not* if it is to saccade either immediately or not at all. There are in fact many examples from recent literature of sensory responses in basal ganglia nuclei that depend on the behavioral setting of the stimulation, and some of these contingencies are quite liberal: there are cells that discharge to sensory stimulation if that stimulation is associated in almost any way with a task that leads to a reward, including when that task involves the withholding of a motor response (NO-GO situations) (Rolls et al., 1983; Kimura et al., 1984; Schultz, 1986; Schultz and Romo, 1986).

It seems clear that such response-contingencies participate in processing beyond simply setting values for the variables of movement execution. But, to conclude that the single-unit findings demonstrate a cognitive function apart from any motor-planning function, is premature. First, single-unit data can not be used to determine the processing role of a structure unless the inputs to that structure have been tested in the same paradigm. For example, in the most thorough study of basal ganglia oculomotor physiology, Hikosaka and Wurtz (1983a-d) identified a number of provocative response-properties for the neurons of the substantia nigra's pars reticulata. When Hikosaka and Sakamoto (1986) tested caudate nucleus cells under the same behavioral tasks, they found similar response-contingencies. In fact, the differences they observed were mainly ones of sign- behavioral 'sets' and stimuli

that elicited decrements in firing rates of nigral neurons led to increments in striatal cells. The point here is that there is no reason to suppose that these contingencies will not also be found in one, or several, of the cortical areas afferent to the caudate nucleus. Because the cortical inputs to any district of striatum are quite widely distributed, this will take years to investigate. And until this is done, single-unit data can only tell us what information is present in the basal ganglia, and not what processing it conducts.

Second, the fact that the information reaching the basal ganglia has been 'cognitively processed', possibly even to the point of modality-independence, does not mean that it is now fodder for further 'cognitive processing'. This information could, instead, be being used in the service of motor planning and execution. This is, in fact, precisely the conclusion of Hikosaka and Wurtz (1983d) to their study of nigral cell firing: "sensory, motor and memory functions are present, not as discrete entities but rather as an interrelated neural organization to produce a saccadic eye movement under specific conditions."

Finally, circumstantial support for the participation of these behaviorally contingent responses in the organization and generation of movements comes from the work of Kimura and colleagues (Kimura et al., 1984). They found striatal units that responded to an auditory stimulus if that stimulus was a cue for delivery of juice. These units were located in the putamen, that is, *in the midst of 'sensory-motor' striatum.* Therefore, if single-unit data is to be taken as evidence for cognitive processing, then the evidence is as good that the putamen is involved in cognition as that the caudate nucleus is[4]. However, most students of basal ganglia

[4]Actually, a participation by the putamen in sensory neglect has been proposed on the basis of monkey lesion experiments by Denny-Brown and Yanagisawa (1976). Their lesions, though, were not clearly restricted to the sensory motor zones of the putamen.

anatomy would reserve at least the putamen for motor programming functions and would ascribe cognitive functions to other parts of the striatal complex, such as the caudate nucleus (see above; Alexander et al., 1986). For this position to be maintained, all currently available single-unit findings must be excluded as being diacritical of cognitive processing.

The behavioral consequence of striatal destruction, in disease or by experiment, have also been adduced as evidence for basal ganglia involvement in cognitive function. Beginning with Wilson's description (1912) of hepatolenticular degeneration, which identified as characteristic of the disease a psychological disorder he termed "emotionalism", clinicians have noted in the symptomatology of extrapyramidal diseases, disturbances that appeared to have cognitive or psychological components not due to the motor problems (see, for example, the Chase et al. volume on Huntington's disease). In addition, nuclei of the basal ganglia have been implicated in diseases not normally thought of as disorders of the extrapyramidal motor system. The most celebrated of these is schizophrenia, for which there is not only long-standing speculation that striatal tissue participates in its genesis (Matthysse, 1974), but also, recently, evidence from positron emission tomographic studies that directly implicates the caudate nucleus (Wong et al., 1986) and the pallidum (Early et al., 1987). The hesitations in concluding from these observations a basal ganglia involvement in cognitive functions are due to: 1) the terribly difficulty with such devastating disturbances of movement in establishing that a symptom is *not* a sequela of the motor defect; and 2) the near impossibility of demonstrating that the pathology of a disease is restricted to the basal ganglia. Interestingly, neuropsychological evidence for non-motoric deficits in Parkinson's disease, after a brief ascendancy (see Teuber, 1976), has recently fallen under serious and considered revisionist attack (Marsden, 1982;

Brown and Marsden, 1986; Rafal et al., 1984). In fact, most recent studies have been able to show consistently and robustly only one disability in patients with Parkinson's disease: their movement time is lengthened (Evarts et al., 1981).

Neuropsychological studies of monkeys with damaged frontal cortex or striatum provide the most compelling account of striatal involvement in cognitive functions. The starting point for these studies, most of which were carried out in the laboratory of H. Rosvold, was the observation that lesions of striatum produce deficits in spatial memory tasks, such as delayed response and delayed alternation, that are also disrupted by ablation of dorsolateral prefrontal cortex (Rosvold and Delgado, 1956; Rosvold et al., 1958; Battig et al., 1960). The prefrontal cortex was known to participate in a topographically organized projection to caudate nucleus (DeVito and Smith, 1964; Nauta, 1964; Cowan and Powell, 1966), so the suggestion emerged that given part of the caudate nucleus will participate in the behaviors characteristic of the cortical region that projects to it (Battig et al., 1960; Johnson et al., 1968). To evaluate this suggestion, one needed behavioral tests selectively sensitive to the integrity of different regions of cortex. Divac et al. (1967) recognized that lesions in the orbital frontal cortex disrupt response tendencies as tested by object reversal, that damage to inferotemporal cortex impairs performance on visual discrimination tasks and that these cortical areas project to regions of the caudate nucleus (ventrolateral head and tail, respectively) that are separate from the anterodorsal part of the head of the nucleus that receives dorsolateral prefrontal input. They therefore damaged in separate monkeys each of these sectors of the caudate nucleus and tested all monkeys on the three tasks: delayed alternation, object reversal and visual discrimination. As anticipated, the animals with anterodorsal striatal ablations were impaired only on the delayed alternation task; those with ventrolateral striatal damage, only on the object

reversal task; and those with lesions in the tail of the caudate nucleus, only on the visual discrimination task.

Because of these dissociations in performance across the subjects, it is clear that the impairments on these "cognitive" tasks are not due to a general motor defect. However, no behavioral dissociation has been found between ablation of the cortical regions and ablations of the sectors of striatum to which they project, save that the striatal deficits are consistently less severe (but see work by Migler referred to in Rosvold and Szwarcbart, 1964). Thus, these experiments can not distinguish between the striatum participating in, say, the formation and retrieval of spatial memory and the striatum forming behaviorally specified channels to the motor apparatus.

This second view was apparently favored by Rosvold. He concluded that the caudate nucleus "appear[s] to be involved principally with the modulation of activity in the motor system which is necessary for an animal to accurately direct his behavior" (Rosvold, 1968). In an examination of how these channels reach the motor system, Johnson and Rosvold (1971) (Johnson and Rosvold, 1971) concluded that, although the dorsal ('delayed alternation') and ventral ('object reversal') sectors of the caudate nucleus have separate targets in pallidum and nigra, the circuits converge, at least in part, in subsequent stages of basal ganglia processing[5].

To summarize my views on the evidence for cognitive processing in the basal ganglia: in spite of the breadth of these researches, which takes in anatomy, single unit physiology, experimental neuropsychology and clinical observation, there is no single line of evidence that clearly demonstrates a basal ganglia involvement in cognitive processing and that at the same time excludes basal ganglia involvement

[5]See also analysis by Percheron et al. (1984) of Golgi material from primate globus pallidus, suggesting convergence in pallidum of inputs from caudate nucleus and putamen.

in planning motor acts that are elicited by tasks requiring cognitive processing for their successful completion. Given the clinical and anatomical evidence, considered in the first part of this chapter, for the basal ganglia as an extrapyramidal **motor** system, it seems most conservative to view the basal ganglia as just that until there is strong evidence to the contrary. It is almost certain, though, that the basal ganglia do participate, at least in part, in a high enough level of motor planning to make the task of teasing motor planning functions apart from cognitive processing ones a difficult job indeed.

DeLong and his colleagues have come to a radically different conclusion about cognitive functioning in the basal ganglia, mainly on the basis of extensive reviews of the anatomical literature (DeLong et al., 1983; Alexander et al., 1986). In their view, the parallel circuits described by Johnson, Rosvold and Mishkin (1968,1971), from different regions of prefrontal cortex to different sectors of caudate nucleus and, in turn, to different pallidal districts, are maintained not only through basal ganglia circuitry, but in subsequent thalamocortical connections. Moreover, among the cortical areas projecting to any given striatal sector, there is (at least) one that is the target of the striato-pallido/nigro-thalamo-cortical connection inaugurated by that sector of the striatum. Thus, there are trans-basal ganglia circuits from cortex to cortex that are closed when analyzed in their essentials, that is, they form a loop. An example of this circuitry would be that of the SMA, which projects to the sensory motor-recipient striatum (in the monkey, the putamen), which in turn establishes a striato-pallido-thalamic connection to precisely that part of ventral thalamus that provides the primary thalamic input of the SMA (Schell and Strick, 1984; Alexander et al., 1986). For DeLong and colleagues, each basal ganglia circuit stands in service of the areas of cortex that project to it. There is, in this account, no overall, or at least no *necessary*, involvement by basal ganglia in the motor

system; it is just that a part of the basal ganglia happens to participate in a 'motor loop' set up by sensory motor and premotor cortex. It follows from this view that if parts of the striatum receive input from cortical areas involved mainly in sensory or cognitive processing (which is the case), then there will be basal ganglia circuits involved in sensory or cognitive (and not motor planning) function. To evaluate this argument, it is perhaps instructive to examine it in a more compelling version, one that clarifies and sharpens the anatomical issues considerably. This version takes as its key the anatomical and functional relationships to the motor system of that part of the striatum most removed, both physically and connectionally, from striatal districts receiving motor cortex input.

The ventral striatum

From work carried out over the past fifteen years, most notably by L. Heimer and his colleagues, it is now accepted that striatal tissue in forebrain is not restricted to caudate nucleus and putamen, but includes the ventrally adjoining nucleus accumbens and olfactory tubercle. Evidence for this inclusion is both histological and connectional. The nucleus accumbens and olfactory tubercle (or 'ventral striatum') virtually duplicate the cytology and the chemistry of the (dorsal) striatum (Heimer and Wilson, 1975; Chronister and DeFrance, 1981). In particular, the high concentrations of dopamine and acetylcholinesterase that are considered diagnostic for striatum in vertebrate forebrain (Parent and Olivier, 1970) are present in ventral striatum (Fuxe, 1965; Jacobowitz and Palkovits, 1974). The connectional organization of the ventral striatum also mirrors that of dorsal striatum. Both receive input from cortex and thalamus, and from the dopamine nuclei of the midbrain and both project to pallidal tissue.

It is the research establishing this last correspondence that secured the idea of a ventral striatum. Heimer and Wilson (1975) demonstrated that fibers from the

nucleus accumbens terminate in basal forebrain in a subcommissural tissue that by its cytology and position appeared to be an extension of the globus pallidus. Moreover, the synaptology of the terminals, as judged by electron microscopic examination, was similar to that seen for striatal endings in globus pallidus. On these grounds Heimer and Wilson designated this accumbens-recipient zone the 'ventral pallidum'. Subsequent studies, particularly with immunohistochemical probes for pallidal neuropil, have certified the correctness of this designation (Switzer et al., 1982; Haber and Nauta, 1983) and most neuroanatomists accept that the striatum-to-pallidum connection is shadowed by a ventral striatum-to-ventral pallidum connection.

Heimer and Wilson suggested that, in parallel with the dorsal pallidal projection to the thalamus, there might be a ventral pallidothalamic connection, possibly with the mediodorsal nucleus of the thalamus. This suggestion has been tested, and confirmed, with modern anatomical tracing techniques (Young et al., 1984; Haber et al., 1985). Thus, parallel dorsal and ventral striato-pallido-thalamic circuits may provide the clearest test of whether there are functionally separate loops through basal ganglia, not all of which are part of an extrapyramidal motor system.

The first issue, then, is whether 'dorsal' and 'ventral' basal ganglia circuits are anatomically separate. Evidence from a number of laboratories suggest that they are not: the nucleus accumbens projects to the substantia nigra pars compacta, the cell group that provides the functionally important dopaminergic innervation of dorsal striatum (Nauta et al., 1978; Swanson et al., 1984). The second issue, does the ventral striatum participate in motor function, has been addressed by pharmacological stimulation of the rat nucleus accumbens (Pijnenburg and van Rossum, 1973; Kelly et al., 1975; Mogenson and Yim, 1981).

These studies have clearly established the functional participation of the ventral striatum in locomotion (specifically, in the regulation of locomotor activity levels). Moreover, recent work indicates that this regulation may be mediated not by intra-basal ganglia connections to motor thalamus, but by the ventral striato-pallido-thalamo-cortical line through the mediodorsal nucleus (Swanson and Kohler, 1986). Unfortunately, there are no comparable studies of ventral striatum in cat and monkey. However, it is known that, in cats and monkeys in which dorsal and lateral striatum have been destroyed, but the ventral striatum and connectionally similar ventromedial caudate nucleus have been spared, administration of L-DOPA leads to hyperkinesia[6] (Harik and Morris, 1973; Kanazawa et al., 1986). Most workers accept that the L-DOPA effect on basal ganglia function is mediated through the striatum. It follows from this assumption that the hyperkinesia observed was produced by those parts of the striatum that were spared. In other words, the ventral striatum and ventromedial caudate nucleus of cats and monkeys also participate in regulating at least some forms of motor activity.

An anatomical approach to the question of striatal processing

There are two separate issues here: 1) are there functionally separate loops through basal ganglia?; 2) are all parts of basal ganglia circuitry geared to controlling motor behavior? It would be bizarre if both propositions were to hold; that is, that it should 'happen' that all basal ganglia loops participate in motor control, but they are essentially separate in their passage through the extrapyramidal system. It seems much more likely that either (A) motor affiliations hold only for a part of striatal circuitry, and other parts of striatum are devoted to other functions allotted according to the cortical input to that part of striatum. In

[6]See also behavioral observations on hyperkinetic syndromes following caudate nucleus destruction alone (Denny-Brown, 1962; Liles and Davis, 1969; Villablanca et al., 1976).

this case, basal ganglia 'loops' are essentially satellites of cortical regions, carrying out homologous tasks for the different regions of cortex, but different functions because the different cortical regions differ functionally. The clinical presentation of basal ganglia diseases as disorders of the extrapyramidal system would then be explained either as a consequence of the large motor representation present in the striatum of primates, or as due to some particularly robust effect of damage to the striatal motor circuit. Or, (B) that the striatum is at service throughout, and at different functional levels, as an extrapyramidal motor system. For this, then, exclusive affiliation with motor system function to make sense, there must be some form of hierarchical and convergent circuitry across basal ganglia structures. Posed in this way, it is clear that the response to the challenge of the parallel loop model of basal ganglia anatomy, as formulated by Alexander et al (1986), is not the enumeration of isolated difficulties with the model, however compelling they may be. What is needed is an *anatomical mechanism* by which the input to basal ganglia can be arranged and processed so that, as output, it is organized to control motor behavior at several levels.

One mechanism could be long-distance association connections within the striatum. However, the anatomical evidence is utterly against this possibility. As a consequence, most students of basal ganglia anatomy anticipate that the locus of convergence, if found, will be in the complex, post-striatal circuitry of the extrapyramidal system. Findings such as that of the existence of projections from the nucleus accumbens to the nigrostriatal cells of the pars compacta (mentioned above), support this view. The approach of this thesis, though, is to examine the first stage of basal ganglia processing, that of inputs to the striatum. The motivations are, first, that there has not been a comprehensive anterograde study of corticostriatal topographies with the modern techniques. In fact, the possibility

has not been excluded that the basal ganglia has wholly separate channels within its circuitry, but carries out convergent functions because of convergence at the level of striatal input, for instance, by a progression of partially overlapping cortical inputs.

The second motivation is findings collected over the last decade about the large-scale internal organization of the striatum. Initial reports indicated that certain afferent fiber systems, including those from cortex and thalamus, are distributed in a patchy manner (Kunzle, 1975; Kalil, 1978; Royce, 1978a). This inhomogeneous fiber-patterning proved to be in large part a reflection of the arrangement of two histochemically distinguished tissue compartments within the striatum: striosomes and matrix (Ragsdale and Graybiel, 1981; Donoghue and Herkenham, 1986; Herkenham and Pert, 1981). Striosomes were first defined in tissue sections stained for acetylcholinesterase (AChE), where they appeared as circumscribed zones of low enzyme activity in a matrix tissue of higher activity (Graybiel and Ragsdale, 1978b). Numerous correlative studies have shown that these AChE-poor striosomes mark out compartments not only in afferent fiber-systems, but also in neurochemically identified cells and neuropil, neurons linked by common birthdates and striatal projection cells (see Chapter 2 for full review). The observation that the projection cells of the compartments have different connections raises the possibility that striatal efferent circuitry may be fundamentally more complicated than parallel striatopallidal and striatonigral projections. But, more important for the issue of parallel basal ganglia pathways, the finding that striatal inputs are compartmentalized, that is, that adjoining striosome and matrix compartments have different inputs, suggests that striatal compartmentalization may be a mechanism for convergence across inputs to the striatum.

The intention of this thesis is to examine the organization of the principal extrinsic afferent connections of basal ganglia. These inputs arise in forebrain, from thalamus and cortex. In addition, because its contribution may be crucial functionally, the amygdalar projection to dorsal striatum will be investigated. The approach will be not just to re-examine thalamostriatal and corticostriatal topographies, but to study how the distributions of afferent fibers are organized with respect to the recently described striatal compartments. The fundamental question to be addressed is whether striatal compartmentalization offers a mechanism by which basal ganglia input from different sources is brought together and whether the topographic and compartmental organizations of striatal afferent connections conspire to set up hierarchies across functionally specified conduction lines to extrapyramidal effector systems.

Chapter 2

The Compartmental Organization Of The Striatum

In 1978 Graybiel and Ragsdale reported that sections from cat striatum treated to show acetylcholinesterase activity displayed regularly spaced, 300-600 μm wide zones of reduced staining distributed in a background matrix of dense stain (Fig. 2-1). By volume, the AChE-poor zones constituted on the order of ten to twenty percent of striatal tissue. Analysis of serial sections stained for the enzyme established that the circumscribed zones seen in individual sections are interconnected and form labyrinths through the striatum.

These zones of low acetylcholinesterase activity appear to be a characteristic feature of the mammalian striatum. They are found in human beings, marsupials, Old World and New World monkeys, squirrels, rabbits and even rats (Graybiel and Ragsdale, 1978a, unpublished). Moreover, the acetylcholinesterase staining method is not the only technique to indicate chemical inhomogeneity in the striatum. In fact most histochemical methods do. As a result of many correlative studies carried out by a growing number of researchers, it is now clear that the histochemical compartments shown by acetylcholinesterase staining are the same as the compartments demonstrated by immunohistochemistry for choline acetyltransferase-, tyrosine hydroxylase-, met-enkephalin-, substance P-, dynorphin-, somatostatin-, neurotensin-, glutamic acid decarboxylase- and calcium binding protein-like molecules (Graybiel et al., 1986; Graybiel et al., 1987; Ferrante and Kowall, 1987; Graybiel et al., 1981; Gerfen, 1984; Graybiel and Chesselet, 1984; Sandell et al., 1986; Goedert et al., 1983; Sugimoto et al., 1987; Graybiel et

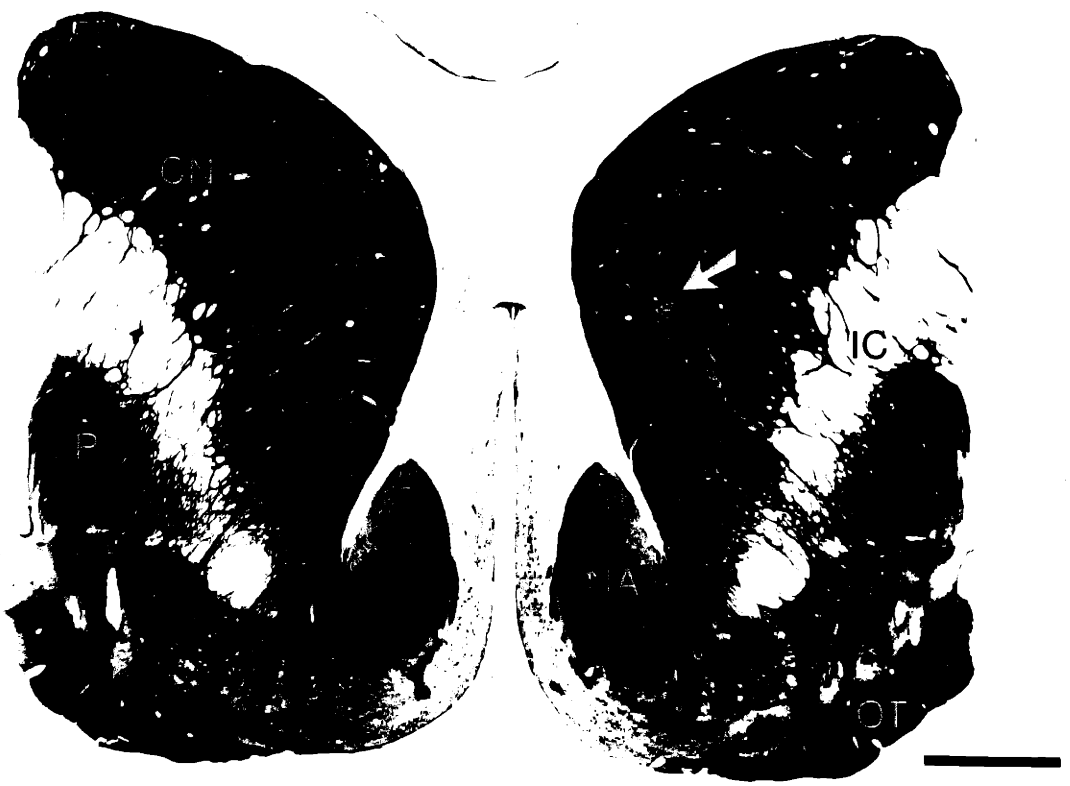
al., 1983; Gerfen et al., 1985), by radiolabelled ligand-based autoradiography for opiate, muscarinic cholinergic (M1), dopaminergic (D1 and D2), neurotensin and benzodiazepane receptors and for choline uptake sites (Herkenham and Pert, 1981; Nastuk and Graybiel, 1985; Nastuk and Graybiel, 1988; Joyce et al., 1986; Loopuijt et al., 1987; Besson et al., 1988; Goedert et al., 1984; Waters et al., 1987; Faull and Villiger, 1986; Rhodes et al., 1987; Lowenstein et al., 1987), and by enzyme histochemistry for butyrylcholinesterase and NADPH diaphorase activities (Ragsdale and Graybiel, 1983; Sandell et al., 1986; Kowall et al., 1987).

Naming the histochemically distinguished striatal compartments

Because of the three-dimensional structure of the AChE-poor zones demonstrated by serial section reconstruction, Graybiel and Ragsdale (1978b) suggested that they be named *striosomes*, for striatal bodies. Although not made explicit at the time, the term *matrix* was used to refer to the extrastriosomal tissue that constitutes the bulk of the striatum.

In 1982, Goldman-Rakic proposed that the primate striatum is made up of two cytologically distinguished compartments- 'islands', which are circumscribed aggregations of striatal neurons seen in Nissl-stained preparations, and 'matrix'. To date, these cytological compartments have been compared only with the distributions of fibers labelled from dorsolateral convexity cortex. These fibers avoid the Nissl islands. It is therefore not directly known whether the cytologically marked striatal compartments correspond to the histochemical ones. There is, though, indirect evidence that the islandic and striosomal compartments are be equivalent: we have found that fibers from monkey dorsolateral prefrontal cortex avoid the striosomes and selectively innervate extrastriosomal matrix (Ragsdale and Graybiel, 1981). Unfortunately, correlative studies on these cytological divisions will be difficult because they are not easily seen or readily outlined in normal adult

Figure 2-1: Striosomes in the caudate nucleus of the cat demonstrated by inhomogeneities in staining for acetylcholinesterase (AChE) activity. Arrow points to one of the AChE-poor striosomes. Abbreviations: CN, caudate nucleus; IC, internal capsule; NA, nucleus accumbens; OT, olfactory tubercle; P, putamen. Section was cut at 50 μ in the coronal plane and stained by the copper thiocholine method, as described by Geneser-Jensen and Blackstad (1971). Scale bar marks 2 mm. Modified from Graybiel and Ragsdale, 1978.


CM
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material: the type case for Goldman-Rakic's cellular analysis was a monkey that had suffered damage to its prefrontal cortex and the compartments are, apparently, not easily identified in intact brains (personal communication).

The other candidate terminology for the histochemically distinguished compartments is *patch* and *matrix*. Patch refers to the histochemical compartment identified in rat caudoputamen by radiolabelling of opiate binding sites ('opiate receptor patches'; Pert et al., 1976). Herkenham and Pert (1981) have demonstrated that the zones enriched in opiate receptors do correspond to AChE-poor striosomes in rat striatum and subsequent correlative studies have confirmed this finding (Gerfen, 1984). Although the term 'patch' for the striosome compartment does have historical warrant, it does not seem advisable. It gives the false impression that any striatal labelling pattern made up of circumscribed patches is patchy because it is observing the histochemically marked striatal compartments. First, although nearly all inhomogeneous histochemical patterns described in the striatum have so far proved, by correlative analysis, to be a reflection of the same histocompartmental organization, this is still a point of fact to be investigated in each instance. Second, an observation of circumscribed 'patches' in the distributions of striatal afferent fibers does *not* predict a selective affiliation with striosomes (see below). Stated differently, the histochemical compartment we call 'striosomes' are, by correlative analysis, an entity. Although the striosomes typically appear in tissue cross-sections as 'patches', this is an attribute of the striosomes and not a sufficient condition for their identification. This difficulty for the 'patch-matrix' terminology could be circumvented by stipulating that 'patch' refers in every instance to the 'patch compartment'; a less cumbersome solution is to give the histochemically marked compartment a distinct designation, such as 'striosomes'.

The cellular organization of the striosomes and the issue of cross-compartmental interactions

There are three lines of evidence distinguishing the cells that reside in the two histochemical compartments. First, immunohistochemical staining of striatum demonstrates that the neurochemical profiles of cells in striosomes and matrix are different. For example, in the dorsal striatum, approximately 50% of the cells in striosomes, but only 25% of the cells in matrix, react with substance P (SP) antisera (Penny et al., 1986; Bolam et al., 1987). (Penny et al., 1986; Bolam et al., 1987) Second, the neurons that make up the two compartments differ in their birthdates. Study of the spatial distribution of striatal cells labelled in ^{3}H-thymidine incorporation experiments has shown that neurons that reside in striosomes are generated over a restricted period of time early in striatogenesis and that most matrix cells are born later (Graybiel and Hickey, 1982; van der Kooy and Fishell, 1987). Third, the neurons that reside in the two compartments differ in the destinations of their axons. The matrical cells project to the two segments of the globus pallidus and to the pars reticulata of the substantia nigra (Graybiel et al., 1979; Gerfen, 1985; Jimenez-Castellanos and Graybiel, 1985). By contrast striosomal cells do not project to these regions. They can, however, be labelled following injections placed in medial substantia nigra (Gerfen, 1985; Jimenez-Castellanos and Graybiel, 1985). Gerfen (1984) has suggested that the nigral targets of the striosomes may in fact be the cell bodies of the dopamine neurons of the pars compacta, but this has not yet been satisfactorily demonstrated.

The finding that both compartments contain striatal projection cells, and that the targets of the compartments are different, raises that issue of whether, and where, convergence between the two compartments takes place. Because it appears to be the exclusive province of the matrical neurons to reach the efferent nuclei of the basal ganglia- the pallidal complex and the pars reticulata of the substantia

nigra (Graybiel et al., 1979; Gerfen, 1985; Jimenez-Castellanos and Graybiel, 1985), it seems likely that the midbrain target of the striosome compartment is some component of basal ganglia circuitry, such as the dopamine cells, that in turn either projects to the striatal matrix or has access to the matrix-affiliated sub-circuitry within the basal ganglia. Unfortunately, there is no evidence one way or the other on this point so far. There is, however, good morphological evidence for local interconnections between the two compartments: the dendrites of both striatal interneurons (including the aspiny neurons containing somatostatin-like immunoreactivity and possibly the large cholinergic cells) as well as those of some of the striatal medium-sized spiny neurons that are thought to be projection cells, have been observed to cross the striosome/matrix boundaries (Gerfen, 1984; Penny et al., 1984; Chesselet and Graybiel, 1986; Bolam et al., 1987). Thus, whatever the processing fate of the striosome-projections out of the striatum, there is good reason to believe that the two compartments interact locally within the striatum.

Striatal afferent fibers are compartmentalized by the striosomal architecture

The afferent fiber-systems of the striatum, including those from cortex, thalamus, substantia nigra and the amygdala, are distributed in a patchy manner (Kunzle, 1975; Kalil, 1978; Royce, 1978a; Wright and Arbuthnott, 1981; Kelley et al., 1982). Ragsdale and Graybiel (1979,1981) and Herkenham and Pert (1981) established that, for cortex and thalamus respectively, at least some of the inhomogeneities in the distributions of striatal projections is due to fibers selectively affiliating one or the other of the histochemical compartments. It was later shown that the nigral input to striatum is also compartmentally organized. Moreover, work in the rat (Moon Edley and Herkenham, 1984; Gerfen et al., 1987) and in the cat (Jimenez-Castellanos and Graybiel, 1987) indicates specific districts of midbrain innervate each compartment. Nigral projections to the

striosomes arise from the region of the A9 neurons (the dopamine-rich cells of the substantia nigra pars compacta), and, in particular, it is ventrally placed A9 cells that are densely aggregated that restrict their striatal projection to the striosomes. The major midbrain projection to matrix tissue arises in the outlying nigral cell groups, particularly A8 in the cat but apparently also A10 in the rat.

Ironically, it is now the striatal projection from the midbrain for which we have the clearest account; there are as yet no comprehensive studies of the striosomal organization of the thalamostriatal and corticostriatal systems. For the thalamus, reports have been restricted to the posterior intralaminar nuclei, which Herkenham and Pert (1981) working in the rat found to project solely to the matrix compartment, surrounding the striosomes in the process. For the cortex, based on data from the cat and monkey (Ragsdale and Graybiel, 1981) and from the rat (Donoghue and Herkenham, 1986), it is clear that projections from the frontal lobe can reach both compartments and that the choice of compartment depends both on cortical region of issuance and striatal region of destination. Both of these studies, however, were preliminary in nature and did not include broad regions of the cortical mantle. And, more importantly, the two studies that have looked beyond the frontal cortex, specifically to sensory cortices (Malach and Graybiel, 1986; Donoghue and Herkenham, 1986), have raised doubts about the generality of the frontal cortex observations: there is a 'patchy' organization to the corticostriatal projection that is restricted to the matrix compartment and that can not be accounted for by the distribution of striosome/matrix borders. Most convincing on this score is the study of Malach and Graybiel (1986), who reported that injections of distinguishable traces placed, respectively, in the deep and the cutaneous receptor regions of cat somatosensory cortex result in interdigitating sets of fiber-patches that are completely restricted to the matrix compartment. Until

the range of cortical areas and thalamic territories studied has been substantially expanded, we will not be able to make any sound, general conclusions about how the major extrinsic afferent systems of the striatum are organized with respect to the striosome system.

A note on compartmentation in the ventral striatum

Striosomes are defined in the dorsal striatum and, from the findings reviewed, appear to be a central feature of that tissue's organization. The nucleus accumbens and olfactory tubercle are considered striatal because they exhibit many of the properties characteristic of dorsal striatum (see chapter 1). However, these shared properties may not extend to the ventral striatum having histochemical compartments equivalent to the striosomes of dorsal striatum: ventral striatal tissue treated to demonstrate AChE activity does not display regularly distributed zones of reduced enzyme concentration. This observation does not necessarily indicate the absence of ventral striatum compartments analogous to the striosome/matrix organization. Although striosomes were initially identified as circumscribed, AChE-poor zones, subsequent correlative studies established that these zones could be seen in many histochemical preparations. This suggests a more general description of the nature of striosomes: they are histochemically *marked* striatal compartments.

Histochemical preparations of ventral striatum do present a tissue of great complexity. Part of this complexity is due to the presence of three major divisions in the nucleus accumbens, divisions that are nearly as signal in their differences as are the nucleus accumbens and the olfactory tubercle. Only once these divisions are recognized is it possible to identify within, or in association with, each division regularly distributed modular structures (see chapter 4 for illustration and a fuller description). In the dorsal division, there are restricted zones enriched in both butyrylcholinesterase (BuChE) activity and SP-like immunoreactivity. In the septal

division, there are circumscribed zones of reduced staining for AChE activity and SP- and met-enkephalin-like immunoreactivity. Along the borders of the ventral division, there are islands of cells that show hardly any BuChE activity. Finally, in the olfactory tubercle and at the medial margin of the nucleus accumbens are the familiar islands of Calleja.

What these tissue compartments share with striosomes is: 1) they are histochemically marked; 2) they make up less than half of the total tissue mass; and 3) they turn out to be connected in three-dimensional reconstructions (Ragsdale and Graybiel, 1987). However, there are a number of difficulties in concluding that these compartments are ventral striatal equivalents to striosomes. First, these compartments are not only not marked by reduced AChE staining (with the exception of the septal division zones), they are not identified by ^{3}H-thymidine autoradiography as early born cell-groups. Second, it may well be that these compartments are too well-marked, both histochemically and cytologically; they may not even be striatal tissue.

One approach to the question of striosome-like compartments in ventral striatum is to better characterize the features that distinguish striosomes from matrix tissue in dorsal striatum. For example, if there were principled connectional grounds by which the afferent connections of striosome and matrix were distinguished, it is possible that these principles could be tested on the organization of the connections and histology of the ventral striatum. For this reason, I will note wherever possible our ancillary observations on the compartmental arrangement of ventral striatum input.

What is the relationship between striosomes and matrix?

I suggested in the introductory chapter that analysis of the differential neural input to striosome and matrix compartments might be crucial to understanding the organization of extrapyramidal conduction-lines. The findings just reviewed suggest that the striosome/matrix distinction is central to the organization of striatal tissue, whether or not it is a mechanism for coordinating trans-basal ganglia pathways. Therefore, whether or not it will solve other puzzles of basal ganglia anatomy, the functional role of striatal compartmentalization needs to be explained. One approach is to this question is detailed anatomical analysis of respective afferent connections of striosomes and matrix: since we know a good bit about the functional roles of the different regions of cortex, the finding of any dissociation in the striosomal distribution of fibers from different cortical areas might suggest in a very natural way differential roles for the two striatal compartments. This approach may contribute to a more general, structural analysis of the striosome system: should the striosomes be regarded as sharing identical functions across striatal districts? or should they be taken as structurally similar devices that are functionally specified according to the region of striatum in which they lie? And, if the striosomes are regionally specialized in some way, is the information processed within adjoining striosomal and matrical tissue closely related (in the way we understand the information reaching the various layers and columns of a cortical area to be) or is the relationship quite distant, and even inconstant across striatal regions?

Chapter 3

Methods

The striatal organization of afferent fibers from amygdala, thalamus and cortex was investigated in the cat by anterograde tracing methods used in combination with the histochemical detection of striosomes. The case material was analyzed by examining tissue sections treated to show the experimentally labelled fibers and by collating these with neighboring sections processed to demonstrate the histochemical compartments.

Experiments were carried out in a total of 116 cats. Injections of distinguishable tracers and bilateral injections permitted multiple deposits in a number of these animals. For the amygdala series, 12 successful deposits were made in 9 cats. For the thalamic experiments, 47 successful injections were carried out in 29 cats. For the cortex series, 71 successful deposits were placed into 53 cats.

Our technique of choice for labelling afferent fibers was the autoradiographic detection of labelled proteins transported orthogradely following the injection of tritiated amino acids into brain (Cowan et al., 1972). Because of reports in the literature that amino acids may vary in their access to transport mechanisms and neural systems (Edwards and Hendrickson, 1981), we used an equal part mixture of labelled leucine and proline in most of our experiments; the only departures were a few cases either employing a proline-leucine-lysine cocktail or consisting of leucine or proline alone. The main drawback we faced with this method was that long exposure times, frequently upwards of six months, were often required to produce sufficient grain-densities in the autoradiograms to permit conclusive comparison with adjacent sections treated to demonstrate striosomes.

^{35}S-methionine and a conjugate of horseradish peroxidase and wheat germ agglutinin (HRP-WGA) were also employed as anterograde tracers. The radiolabelled methionine could be substituted for leucine and proline in the autoradiographic experiments (Graybiel, 1975). This higher energy isotope permitted a dramatic reduction in required exposure times and was of special value in studying connections of low volume, such as the amygdalostriatal projection. The cost of this sensitivity was a sharp increase in background relative to signal, which was particularly confounding for the analysis of injections sites, and a reduction in the resolution of the microscopic grain-figures. For these reasons, and because methionine has not been tested as a neural tracer in as many systems as have proline and leucine, it was not used routinely but only as required.

The HRP-WGA molecule has proved an expeditious and extremely sensitive tracer when stained by peroxidase histochemistry that employs tetramethyl benzidine as a chromagen (Mesulam, 1978; Mesulam, 1982). Its value is severely handicapped, though, by the exuberance of its intracranial transport. Amino acid-based methods might produce false positives due to anterograde trans-synaptic transport, but there is no good evidence that intact or damaged fibers passing through an injection site can acquire this label. A 'fibers-of-passage' concern is, however, a major issue for all HRP-based studies. Moreover, HRP-WGA has been documented as travelling trans-neuronally in both anterograde (Gerfen et al., 1982; Itaya and Van Hoesen, 1982; Itaya et al., 1986) and retrograde (Harrison et al., 1984; Porter et al., 1985) directions and as probably engaging in even more extended interneuronal trafficking (Itoh et al., 1984). Finally, and of particular concern for anterograde studies of highly interconnected forebrain circuits, free HRP (and, therefore, probably the conjugate too) can be readily transported across the collaterals of labelled neurons (de Olmos and Heimer, 1977). These interpretive

difficulties caused us to limit our use of this tracer to preliminary investigations or experiments requiring a second label.

All tracer-substances were dissolved in sterile saline. The HRP-WGA conjugate (Sigma) was constituted to a 10% or 33% solution. The radioisotopes (New England Nuclear Corp.) were concentrated to 150-250 μCi/μml in the ^{35}S-methionine preparations and to 40-250 μCi/μml (typical case: 150 μCi/μml) for the ^{3}H-amino acid material.

Surgical Procedures

Healthy, adult cats of both sexes underwent intracranial surgery to deliver the labelled tracers. They were anesthetized by one of two procedures. In the early experiments the animals were given 30 mg ketamine hydrochloride (Ketaject, Ketaset) and then deeply anesthetized by intravenous injection of sodium pentobarbital (Nembutal). Anesthesia was maintained with supplemental doses of the barbiturate delivered into the peritoneum. In later experiments the cats were anesthetized with a mixture of 13 mg/kg ketamine hydrochloride and 0.6 mg/kg xylazine (Rompun). This dose was repeated as necessary to attain and sustain deep anesthesia. In no surgery was administration of more than four mixtures required. These animals were also given 0.2 mg atropine and 0.4 mg dexamethasone (Azium).

The anesthetized cat was mounted in a Kopf stereotaxic apparatus; its scalp was incised and, in restricted cases demanding exposure of insular or temporal cortex, some muscle cut. The skull was opened with a bone cutter or a trephine. When required, the hole was then enlarged with a bone rongeur. The dura mater was slit and, in some of the experiments involving cortex of the mesial wall, a hemisphere retracted with a spatula used in combination with cottonoid patties soaked in sterile saline.

All deposits of tracer substances were made with a 1 μl Hamilton syringe

given a beveled tip. For the amygdala and thalamus and some of the cortex cases, the syringe was mounted on a stereotaxic device, positioned with reference to previous case and atlas coordinates and to sulcal and bony landmarks, and guided into brain vertically approach or at an angle of 16° or 45°. The syringe was hand-held only for those cortical injections where the area of interest could be seen and the syringe carrier could not be easily positioned.

Deposits made under stereotaxic guidance were placed in one, or at most two, sites per hemisphere. The volume delivered at each site was from 80 to 180 nl (except for two cases of perirhinal cortex injection where it was 270-280 nl). For the cortical cases, injections were typically made at several sites and sometimes at as many as ten separate locations. The deposits at each site varied in volume from 40 to 100 nl (and in one case to 140 nl). The total amount of tracer delivered was usually about 500 nl but the range was 150 to 750 nl. Care was taken to flush the cortex with sterile saline between injections in order to dilute any label that may have escaped from the place of deposit.

After all the deposits of tracer had been placed, the cortex was protected with gelfoam, if a bone flap had been turned it was replaced and the wound-tissue was closed in layers. Cats were injected with up to 300,000 units of penicillin and fed subcutaneously with lactated Ringer's solution until they had recovered from the surgery.

The animals were allowed survival periods of two to seventeen (and, in single cases, twenty-one and twenty-seven) days. They were then deeply anesthetized with a lethal dose of Nembutal and perfused transcardially. The perfusate in the model case consisted of one-half liter of heparinized saline, followed by three liters of a 0.1M dibasic phosphate-buffered saline (PBS) solution containing 4% paraformaldehyde and 4% sucrose(w/v), and then by one liter of 4% sucrose in

PBS. This final liter was often cooled to 4°C. For some of the animals injected with HRP-WGA, the fixative was a mixed aldehyde solution that ranged in strength from 1/4% glutaraldehyde and 4% paraformaldehyde to 2% glutaraldehyde and 1/2% paraformaldehyde. Variations on these protocols included omission of the initial saline flush or its replacement by PBS, reduction of the volume of fixative to two liters, reduction or omission of the sucrose-PBS rinse, and increases in the sucrose concentration up to 10% in the final liter of perfusate.

Histology

All brains were blocked in the transverse plane and washed for one to four days in a PBS solution containing sucrose in ascending concentrations of up to 30%. Sections from the brains were cut at 30 or 40 μm on a freezing sledge microtome and collected in 0.1 M phosphate buffer. Tissue not processed directly was stored in a phosphate buffered solution containing 0.1 M sodium azide.

Sections from the autoradiographic cases were postfixed, rinsed extensively, mounted on glass slides, dried and defatted. The slides were dipped in Kodak NTB-2 emulsion diluted by half with a 0.1% Dreft detergent solution, and stored with desiccant in the freezer. After varying intervals of exposure, the autoradiograms were developed in Kodak D-19 at 12-16°C and counterstained with cresyl violet. Although we allowed exposure times to range from three days to ninety-six weeks, our standard practice was to prepare two sets of autoradiograms, each of which included a one-in-twelve series of sections through the injection site and the striatum. One of the sets would be exposed for a fixed period of time, which we chose to be three days or one week for the ^{35}S-methionine experiments and four weeks for the ^{3}H-leucine cases. The other set was exposed as long as proved necessary either to convince us that the striatal projection in that case was minor or that the case was unsuccessful, or to produce a fiber-pattern of sufficient

strength as to permit an informative comparison with adjacent sections treated to demonstrate the histochemical compartments.

The peroxidase activity of the HRP-WGA complex was demonstrated by histochemical procedures that have tetramethyl benzidine (TMB) as the primary chromagen. In our initial experiments the tissue was treated according to the revised protocol of Mesulam (1982). For most of our material, though, we adapted a modification suggested by Illing and Graybiel (1985): incubations were extended to from forty to eighty minutes and were carried out in cooled solutions in the dark. The solutions were changed four to seven times over the course of the reaction and with each change the concentration of peroxide was monotonically increased until it reached a final level of 0.003-0.01%. Some sections in selected cases were then treated with the diaminobenzidine-based stabilization procedure for TMB-processed tissue (Rye et al., 1984). As a rule the TMB-labelled sections were not counterstained; after air-drying, they were swiftly dehydrated in alcohol, defatted and coverslipped with Eukitt mounting medium.

In all successful cases, sections serially adjoining those processed to show the transported label were reacted to display the striosomes. Acetylcholinesterase (AChE) staining was done for every experiment as this is the most reliable and best characterized way to demonstrate the histochemical compartments. It is not, however, the best method for all regions of the striatum, nor is it necessarily the best method for a given cat. Consequently, in many of the cases we also stained serial neighbors for the presence of substance P-like (SP-like) immunoreactivity as this method can be conspicuous in demonstrating striosomes in dorsolateral and caudal districts of the caudate nucleus where AChE staining is often rather homogeneous. Other procedures, including staining for met-enkephalin-like immunoreactivity, for NADPH-diaphorase activity (often good for showing

striosomes in the dorsomedial caudate nucleus) and for butyrylcholinesterase (BuChE) activity (particularly informative about histochemical compartments in the ventral striatum), were recruited as needed.

For the AChE enzyme histochemistry we used the copper thiocholine technique (Koelle, 1954) in the two-stage procedure described by Geneser-Jensen and Blackstad (1971). To stain for BuChE activity we replaced acetylthiocholine iodide, the substrate of the AChE-reaction solution, with 9.5mM butyrylthiocholine iodide and substituted 1mM BW284c51 (Burroughs Wellcome), an inhibitor of AChE, for ethopropazine hydrochloride (Parsidol, Warner-Chilcott), an inhibitor of BuChE (Koelle, 1954; Shute and Lewis, 1963). For reactions done on striatal tissue the product was developed with a 10% solution of potassium ferricyanide. In some cases we also stained brainstem tissue for AChE activity to help us identify nuclear boundaries there; the reaction product in this material was demonstrated with the silver-sodium sulfite recipe of Hardy et al. (1976). The nitro-blue tetrazolium salt method as described by Sims et al. (1974) was followed to stain striatal tissue for NADPH-diaphorase activity.

Tissue sections destined for immunological reactions were first treated to five minutes of a 10% methanol/3% hydrogen peroxide solution followed by five minutes of a 0.2% Triton X-100 wash and thirty minutes in a solution containing normal goat serum diluted 1:30. Substance P-like immunoreactivity was then probed with rabbit anti-SP serum provided by Dr. R. Ho (6G, diluted 1:250 or 1:1000); enkephalin-like immunoreactivity, with rabbit anti-met-enkephalin serum provided by Dr. R.P. Elde (R153H, diluted 1:500 or 1:600). The primary incubation was carried out for several days at 4°C in the presence of normal goat and cat sera. This was followed by two thirty minute treatments at room temperature with (A) goat anti-rabbit IgG at a 1:10 dilution and (B) rabbit

peroxidase-antiperoxidase reagent (PAP) diluted 1:30. Following a rinse with a cobalt chloride solution the PAP was demonstrated with diaminobenzidine-based peroxidase histochemistry. The staining in selected sections was further enhanced by fixation in 0.1% osmium tetroxide. For all treatments, solutions were prepared in 0.5M Tris buffer containing 0.9% saline and the progress from one step to the next was standardly interrupted by buffer washes (Graybiel et al., 1981; Graybiel and Chesselet, 1984; Sternberger, 1979).

In all autoradiographic cases, the distribution of grains in the autoradiograms was compared with the pattern of AChE staining seen serially adjoining sections. It was not possible to carry out both procedures in the same section because of a negative chemographic interaction between the copper ferrocyanide of the cholinesterase method and the emulsion used for autoradiography. This reaction was particularly damaging to the enzyme stain. We reasoned that a physical barrier between the AChE-stained section and the coat of emulsion would prevent the contact chemical reaction, but not the desired radiochemical one, if the decay particle of the radioisotope were of sufficient energy to penetrate the barrier, and ^{35}S-methionine appeared to be a good candidate for such a label. Sections were stained for AChE activity and were then prepared for autoradiography as outlined above. After defatting, the sections were dehydrated to absolute alcohol, dipped briefly in an ether/alcohol solution (equal parts) containing 1% celloidin, hardened in 80% alcohol and rehydrated. The tissue was then processed for autoradiography. After development of the emulsion, the sections were directly dehydrated, cleared in xylene and coverslipped, with care taken in the 95% and 100% alcohols to add a few drops of chloroform to prevent lifting of the coat of celloidin.

With this protocol we saw no evidence of chemographic interaction. A moderate increase in exposure time was necessary for the celloidin-treated material

to produce an accumulation of silver grains comparable to that observed in untreated material. The total exposure time, though, was still well within the range expected for sulfur-35, as opposed to tritium, autoradiography. Under darkfield and lightfield illumination the Hatchett's brown of the AChE stain could be readily distinguished from the reduced silver grains of the autoradiograph, particularly under high power examination.

Data Review and Presentation

All slides were examined with lightfield illumination. The autoradiograms and the TMB-reacted sections were also studied under darkfield optics. Inspection and photography of the latter material was greatly aided by the use of crossed polarization filters inserted in the light path (Illing and Wassle, 1979).

Serial comparisons between the histochemical and the experimentally labelled material were based on the pattern of blood vessels and neuroanatomical landmarks. Where necessary to confirm an analysis, the distribution of labelled fibers was charted onto an enlarged tracing of a section's outline, nuclear boundaries and vascular profile. Guided by these fiducial markings, the charting was aligned with macroprojections, or with comparable drawings, of adjoining sections treated to show striosomes.

Many of the cortical injection sites were translated from the processed slides to projections onto lateral, dorsal or medial views of the cat's cerebral hemisphere. The sulcal patterns of the medial views were reconstructed from the tissue sections while those of the other perspectives were based on photographs taken of the brains before sectioning.

To ease comparison across the cases of this thesis, all data displayed is presented as though the primary deposits of label were placed in the left hemisphere.

Chapter 4

The Amygdalostriatal Connection

Of the four great cellular masses of the forebrain, three of them, the cortex, the thalamus and the amygdala, are known to be directly interconnected in highly specific ways. The fourth structure, the striatum, does receive projections from each of the other three, yet its return connections travel in large part by indirect paths that lead through the globus pallidus and substantia nigra. It has long been a goal of anatomists of forebrain circuitry to discover the course and specificity of these reciprocating lines. The classic approach to this problem has been to establish the presence and then to study the topography of internuclear connections among basal ganglia structures and their brainstem targets (Nauta and Mehler, 1966; Kemp and Powell, 1971d; Graybiel and Ragsdale, 1979; Mehler, 1982). Recent disclosures concerning a compartmental organization to the striatum suggest, instead, that a first task must be to understand the intrastriatal disposition of extrinsic afferent fibers in relation to its compartmental ordering (see chapters 1 and 2).

The connections of the amygdala, because they are more limited than those of thalamus and cortex, present an especially attractive vantage point for inquiry into this question. Unlike the thalamus and cortex, the amygdala does not project throughout the striatum, but densely innervates the ventral striatum (nucleus accumbens and olfactory tubercle) and projects more weakly to medial and ventral parts of the dorsal striatum (caudate nucleus and putamen) (Krettek and Price, 1978a; Kelley et al., 1982; Russchen et al., 1985). It is similarly more restricted in its connections with other parts of the telencephalon; it serves as the hub of one of

two largely separable circuits, the other being hippocampal, that constitute the limbic system at the level of cortex and thalamus (Nauta, 1962). Behavioral studies are consistent with this anatomy in suggesting that the functions of the amygdala, though vital, are more circumscribed than those of thalamus and cortex (Kluver and Bucy, 1939; Aggleton and Mishkin, 1983).

Given anatomical and behavioral evidence for a specialized functional domain to amygdalar circuitry, we wondered whether the amygdala might selectively innervate one or the other of the striatal tissue compartments in its projection to dorsal striatum. We knew that Kelley et al. (1982) in the rat and Russchen et al. (1985) in the monkey had found that amygdalostriatal fibers are not evenly distributed, but are instead arranged as patches. A 'patchy' projection, however, does not in itself indicate a connection with either the striosome or the matrix compartment (Malach and Graybiel, 1986). We therefore compared the distribution of amygdalostriatal fibers to the arrangement of the striosome system as identified in material stained for AChE activity. We also examined the compartmentation of the amygdalar projection to the ventral striatum.

The projection to dorsal striatum was not reported by Krettek and Price in their classic autoradiographic papers on amygdalar efferent connections, probably because it is not a dense projection and is consequently not detected in autoradiographs whose exposure to tritium-labelled material is restricted to two weeks (Krettek and Price, 1977a). Kelley et al. (1982) in their study overcame this technical limitation by using prolonged exposure times on the order of three to four months. We have chosen instead to employ two more sensitive anterograde tracers that do not require extreme processing times to demonstrate the amygdalostriatal projection: horseradish peroxidase conjugated with wheat germ agglutinin (HRP-WGA) (Mesulam, 1982) and the high energy radiolabelled amino acid ^{35}S-methionine (Graybiel, 1975).

Results

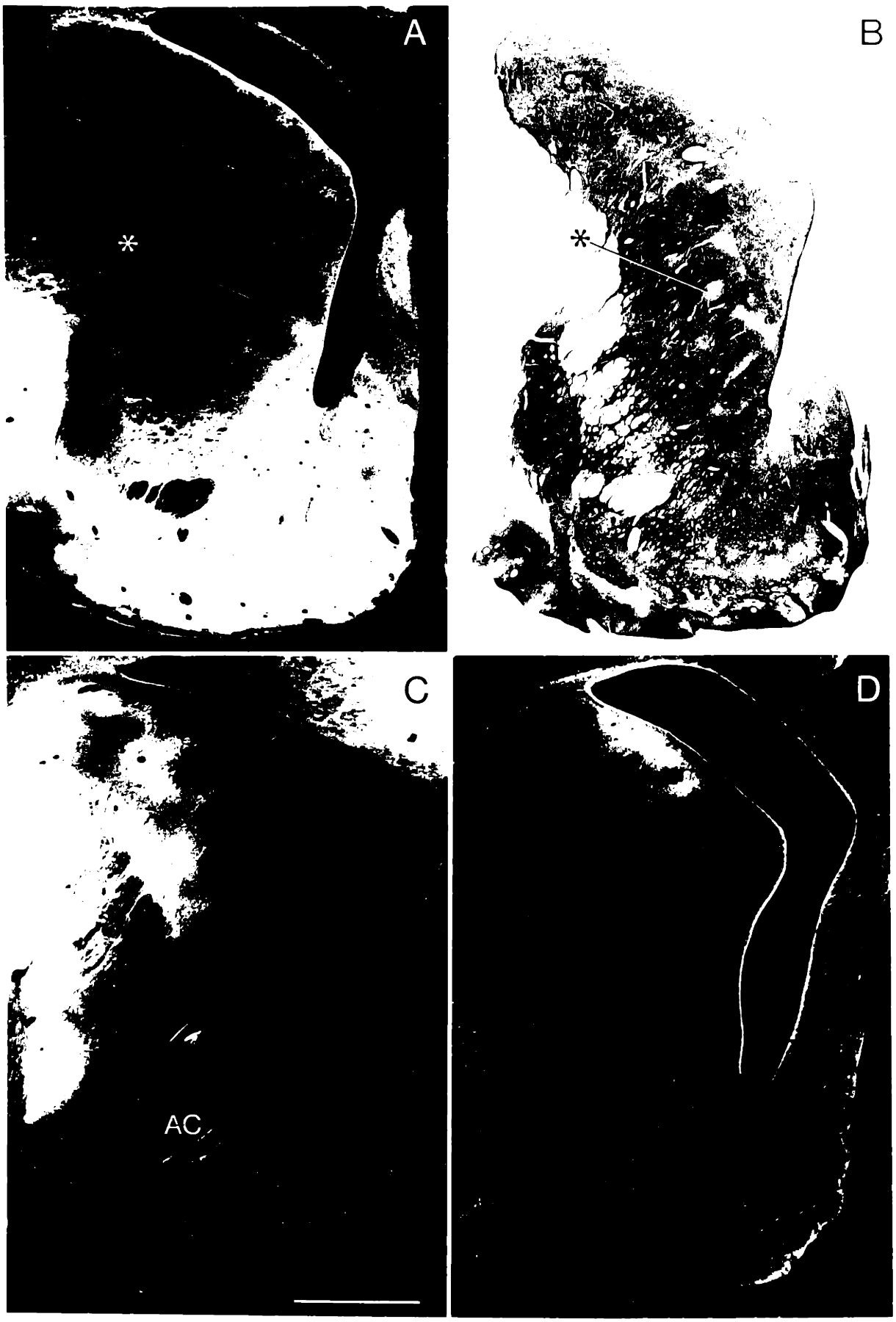
Observations with large deposits of HRP-WGA. For our initial study of the amygdalostriatal projection-system we made massive deposits of HRP-WGA into the amygdala and used the tetramethylbenzidine (TMB) histochemical procedure of Mesulam (1978) to demonstrate the transported label. Figure 4-1 shows a pair of serially adjoining sections taken from case CHAm-1 and prepared for peroxidase (A) and acetylcholinesterase (B) histochemistry. In this cat the conjugate was delivered bilaterally and, on the side illustrated, we used an angled approach to the amygdala in which the injection needle passed through the lateral overlying cortex. TMB reaction-product was distributed throughout the amygdala, but the deposit was centered in the basolateral complex.

The labelling of amygdalofugal fibers, though heaviest in the ventral striatum, was also quite pronounced in the ventral half and the medial edge of the caudate nucleus (Fig. 4-1A). By contrast, label was almost absent from dorsal and lateral parts of the caudate nucleus and dorsal putamen. This suggested a strong confirmation of Kelley et al. (1982)'s proposal from rat experiments that amygdalar fibers are excluded from that portion of the caudate-putamen in receipt of fibers from sensory-motor cortex. To test this claim further in the cat, we made injections into pericruciate cortex massive enough to cover most or all of area 4γ. Figure 4-1C illustrates a section taken from such a case at a transverse level similar to that presented in panel A. It is clear from the comparison of Figures 4-1A and 4-1C that the striatal region targeted by fibers from motor cortex is essentially free of afferent connections from the amygdala. At successively more dorsolateral levels, however, the amygdalar labelling tended to peter out rather than to terminate abruptly, suggesting that there may be zones adjoining the sensory-motor district that are impoverished of amygdalar fibers.

Abbreviations

AC	Anterior commissure
AmH	Amygdalohippocampal area
bi	Border island of the nucleus accumbens
BL	Basolateral nucleus of the amygdala
BM	Basomedial nucleus of the amygdala
Cla	Claustrum
CN	Caudate nucleus
dmv	Dorsomedial segment of the ventral division of the nucleus accumbens
Ce	Central nucleus of the amygdala
Ep	Entopeduncular nucleus
GP	Globus pallidus
iC	Island of Calleja
IC	Internal capsule
L	Lateral nucleus of the amygdala
NA	Nucleus accumbens
OT	Optic tract
P	Putamen
v	Ventral division of the nucleus accumbens

Figure 4-1: Topographic and compartmental features of the amygdalostriatal projection demonstrated with HRP-WGA as an anterograde tracer. A and B, Photomicrographs of serially adjoining sections prepared for TMB histochemistry (A) and AChE staining (B) from the striatum of cat CHAm-1 in which HRP-WGA was deposited in basolateral amygdala. Asterisk indicates spatially correspondent fiber-rich and enzyme-poor zones. C and D, Labelling at a comparable striatal level produced by injections into sensory-motor cortex (C: case CHMC-1) and posterior parietal cortex (D: case CHRC-13). Intense labelling of ventricular edge is artifactual (see D). Scale bar marks 2mm.

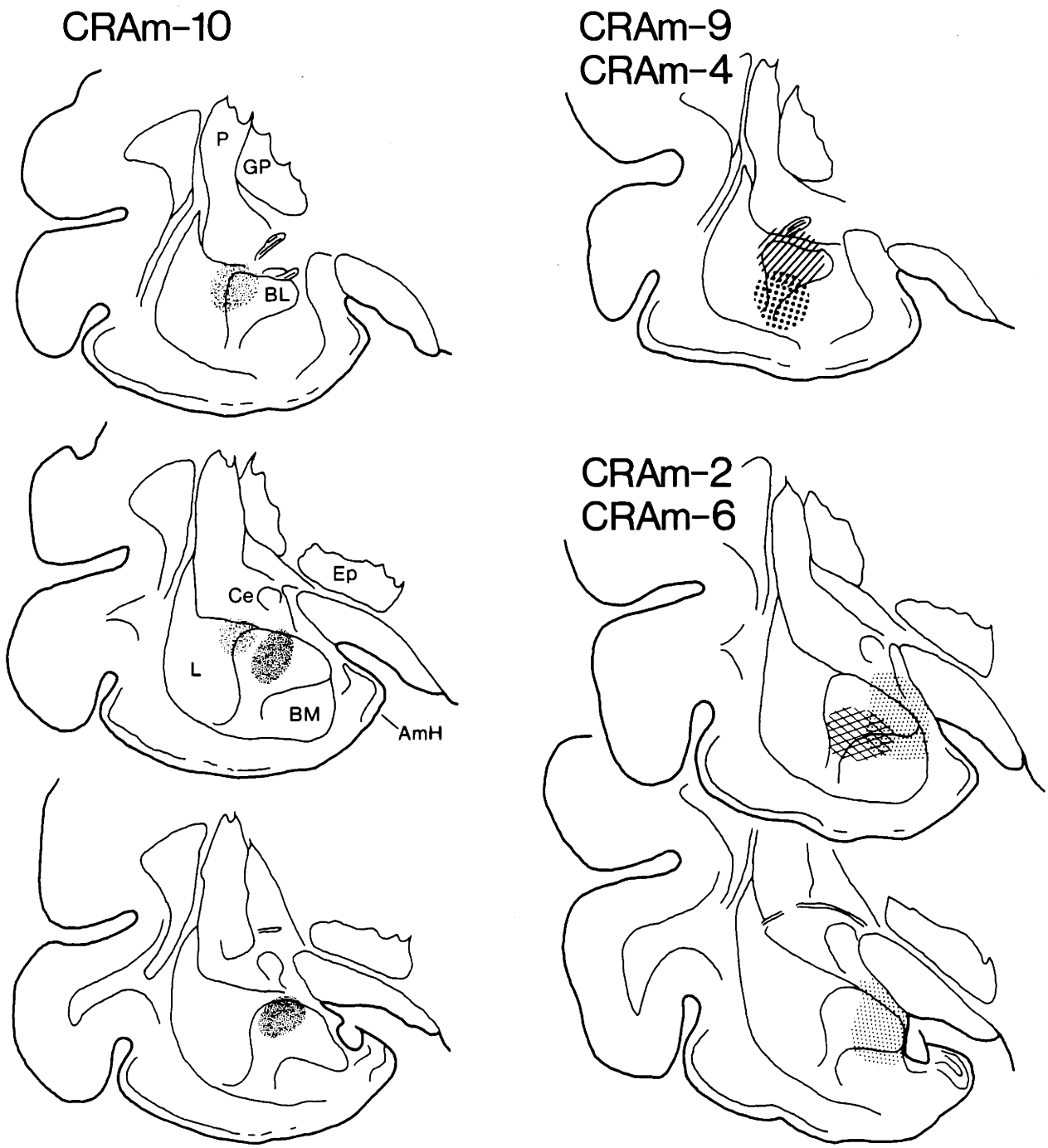

A
B
CN
*
*
NA
C
AC
D

The experimental findings illustrated in Figure 4-1D suggest one cortical system targeted for this intermediary striatal region. The labelling shown was elicited with injections of HRP-WGA that blanketed the crown of the suprasylvian gyrus (cortical area 7). Comparison of panel D with panels A and C in Figure 4-1 suggests that parietostriatal fibers terminate in a dorsomedial striatal district that lies between a periventricular strip that receives fibers from basolateral amygdala and the lateral zone of sensory-motor fiber-terminations. Amygdalostriatal fibers, then, not only avoid the sensory-motor sector of the striatum, but also, apparently, that district innervated by visually-affiliated parietal cortex.

Within the field of termination of the amygdalostriatal projection, the distribution of amygdalar fibers was quite heterogeneous, and in the caudate nucleus the arrangement was as a set of regularly spaced patches of differing shape, roughly one-half millimeter in cross-sectional width. Comparison of serially adjoining sections stained for HRP-WGA and acetylcholinesterase (AChE) activity established a precise correspondence between the fiber-rich zones of the amygdalar projection and the AChE-poor striosomes (see Fig. 4-1A,B). The only important differences observed were that the amygdalar patches appeared more connected, by weak labelling, with one another and with a strip of HRP-WGA label that stretched along the medial edge of the caudate nucleus. This strip did not have a correlate in the AChE-stained material.

The interpretative difficulty of this result is that HRP-WGA tracing studies risk false positives produced by transneuronal transport or by axonal uptake by neuronal processes that pass through or terminate in the amygdala ('fibers-of-passage' and 'cross-collateral' transport). For these reasons we sought to confirm our initial observations with the autoradiographic method, employing as our main tracer the radiolabelled amino acid ^{35}S-methionine.

Figure 4-2: Chartings of the injection sites for five autoradiographic cases described in this study. Selected coronal sections appear, from top to bottom of the page, in rostral to caudal sequence. Placement of the two injections in case CRAm-10 are shown on the left. Topmost illustration on the right depicts the deposits for cases CRAm-9 (upper site) and CRAm-4 (lower site). The injection sites for cases CRAm-2L and CRAm-6 are respectively described in the upper and lower portions of the middle panel on the right, while the caudal continuation of the CRAm-2L deposit is presented in the lower panel.


CRAm-10
P
GP
BL
Ce
Ep
L
BM
AmH
CRAm-9
CRAm-4
CRAm-2
CRAm-6

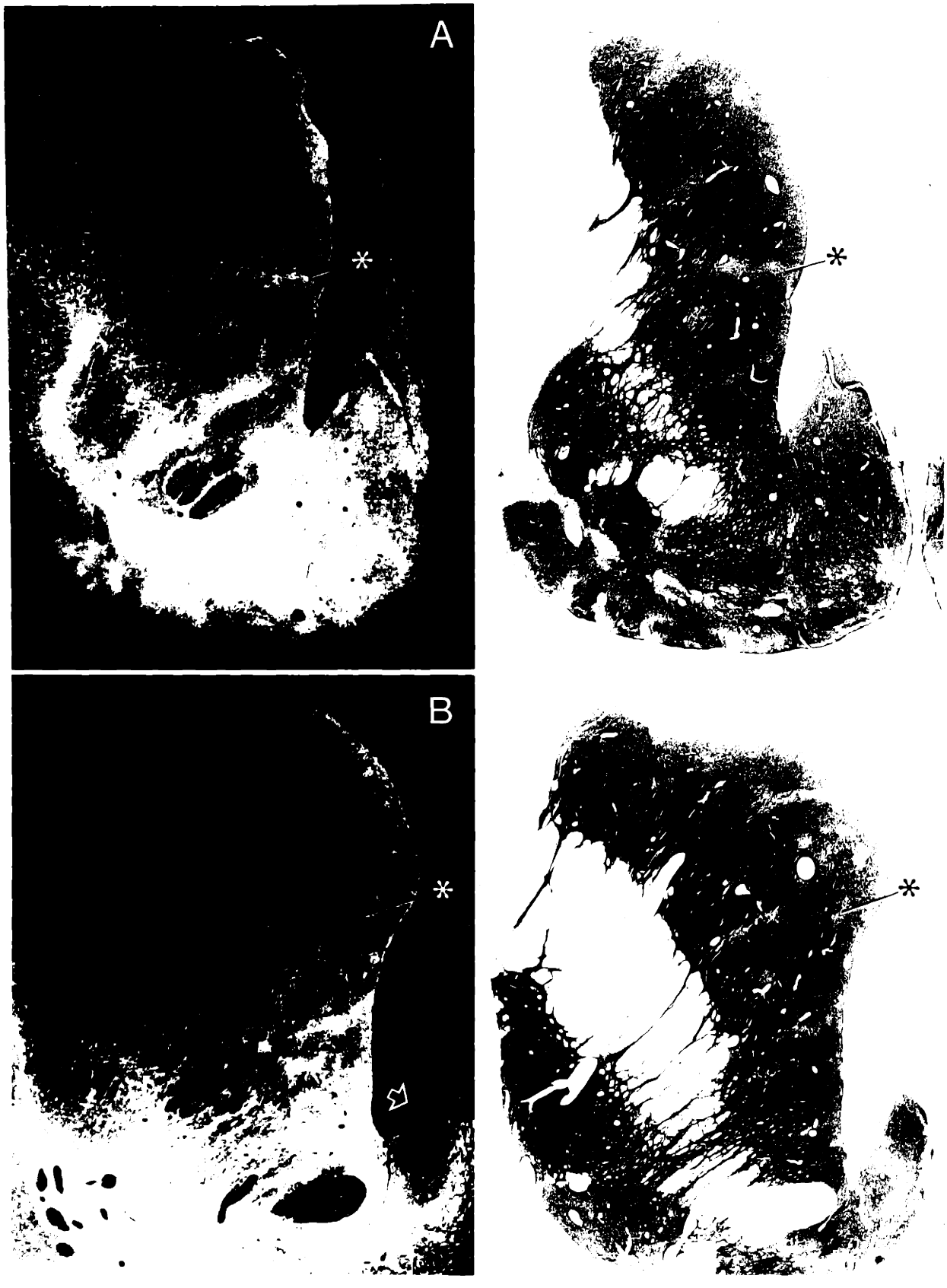
Observations with smaller deposits of radiolabelled amino acids. Illustrated in Figure 4-2 are injection sites from five of the autoradiographic cases. We found, with ^{35}S-methionine as a tracer, that autoradiographs of the injection sites, when exposed for times comparable to those used to trace labelled fibers in the same material, had an extended field of heavy, diffuse label. In the cases reported here the labelling often included much of the amygdaloid complex and overlying cortex. With brief exposure times (*ca.* three days), we found that the injection sites, viewed in lightfield optics, appeared relatively limited in size and, more importantly, that the cross-experiment variations in the distribution of efferent fibers could be reasonably accounted for by the variations in the distribution of these more restricted zones. It is these "effective injection sites" that are marked in shading in the chartings of the tracer deposits.

For our chartings and analysis we relied on the AChE staining method to establish the borders of the amygdaloid nuclei and, to outline the basolateral nucleus, we have taken the "almost universal agreement" that this magnocellular part of the basal nucleus stains intensely for the enzyme AChE (Hall, 1972). In the cat, AChE activity in this nucleus is not evenly distributed but is somewhat impoverished in its medial core at mid-anterior-posterior levels (see Figure 4-7-right side and Russchen, 1981). This inhomogeneity was not a problem in outlining the nucleus. The limits of the basolateral nucleus demonstrated in AChE preparations may not precisely correspond to those drawn by Krettek and Price on the basis of Nissl-stained material. In particular, a zone containing large cells that we, by the evidence of AChE staining, would place in the dorsolateral basomedial nucleus they, by cytological analysis, appear to identify as a rostral extension of the posterior basolateral nucleus (Krettek and Price, 1978b: their Fig. 3). These differences were not significant in the interpretation of the case-material.

Case CRAm-10. The largest deposits of radiolabelled tracer in this series of experiments were placed in the amygdala of cat CRAm-10. Two injections were made: an anterior one spanning the border between the dorsolateral quadrant of the basolateral nucleus and the laterally adjoining lateral nucleus of the amygdala, and a posterior one centered in the dorsal portion of the basolateral nucleus (Fig. 4-2). This resulted in massive and inhomogeneous fiber-labelling throughout most of the striatum. As can be seen in the three pairs of adjacent sections shown in Figure 4-3, there was a remarkable correspondence between the patches of amygdalar fibers labelled in the autoradiographs and the striosomes weak in AChE activity. In addition, with the combined AChE staining and autoradiography procedure, we were able to confirm heightened grain-levels within the enzyme-poor zones in single tissue sections (not illustrated). From this experiment and the observations using the lectin-peroxidase conjugate, we conclude that fibers from the basolateral nucleus of the amygdala innervate striosomes throughout their area of termination in the caudate nucleus.

The labelling in case CRAm-10 was quite similar to that observed in the HRP-WGA experiments. For instance, the patches of amygdalar fibers appeared much more connected with each other than did the AChE-poor striosomes and there was labelling of a strip of caudate nucleus stretching along its ventricular face. The labelled fibers were largely excluded from the dorsolateral quadrant of the caudate nucleus (Fig. 4-3A-C) and the anterodorsal putamen (Fig. 4-3A,B). Some fibers, however, were seen to travel around the dorsolateral rim of the caudate nucleus and within the subcallosal fasciculus, and a very few fibers could in fact be detected in the dorsolateral quadrant itself (these also lay in the AChE-poor zones). It is possible, then, that an injection of a very sensitive retrograde tracer into the dorsolateral striatum might produce retrograde cell-labelling in the basolateral nucleus of the amygdala (Fass et al., 1984).

Figure 4-3: Relation between amygdalostriatal fibers and the striosomes seen following most extensive deposit of radioactive tracer into the basolateral nucleus (case CRAm-10). Photomicrographs are of pairs of serially adjacent sections taken at rostral (A), intermediate (B) and caudal (C) levels and prepared for autoradiography (left) and AChE histochemistry (right). Single asterisks mark correspondences between patches of labelled amygdalar fibers and AChE-poor striosomes. Double asterisks in C indicate match in the dorsal putamen between a grain-poor zone and an enzyme-weak striosome. Note prominent labelling of tissue along the ventricle (A-C). Open arrow in B notes absence of fibers from the caudomedial nucleus accumbens. Straight arrow in C points to a region of reduced fiber-labelling in ventral putamen. Section in C stained for AChE subsequently processed for autoradiography (see methods). In lightfield, dorsal cap of injection site is visible (curved arrow). Scale bar: 2mm.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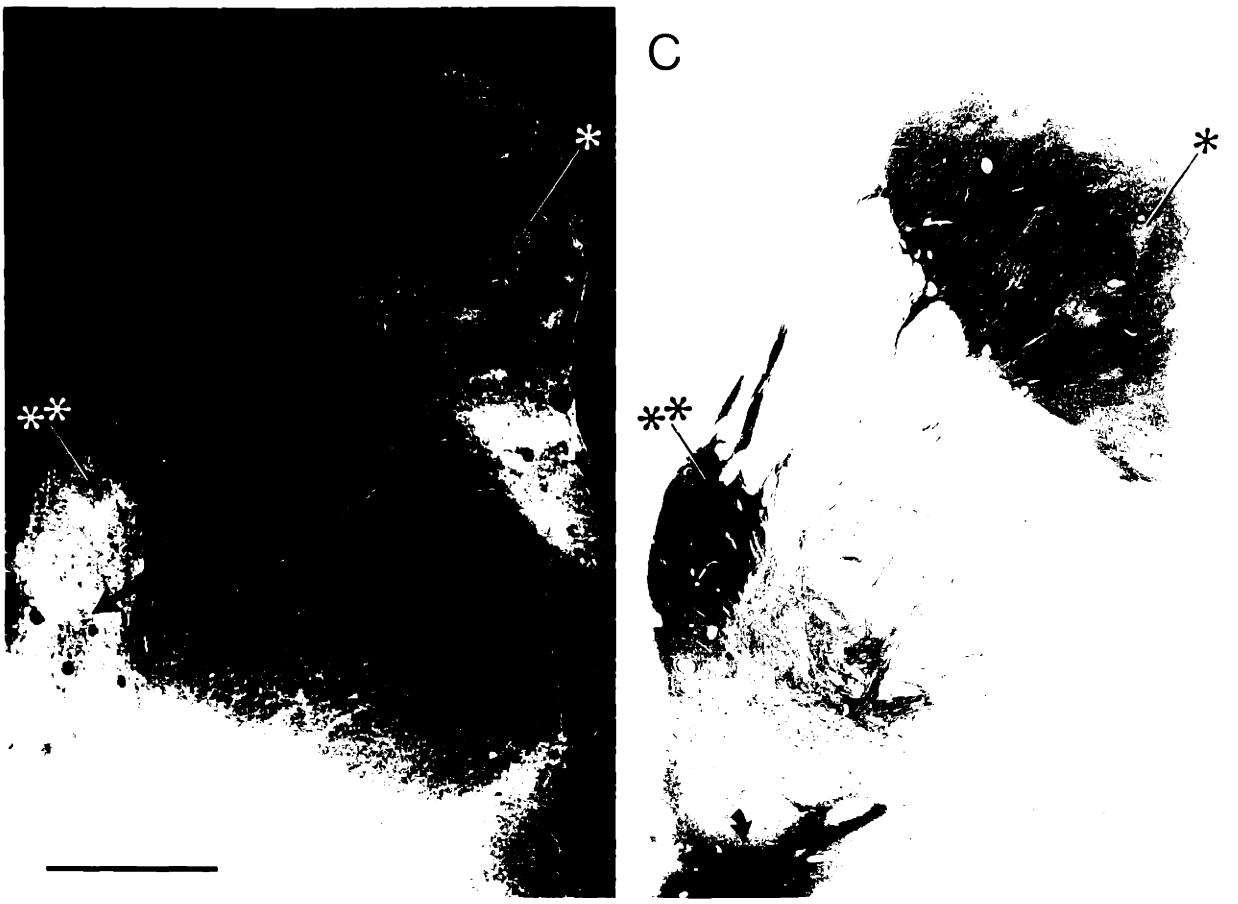
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At posterior levels of the striatum, the amygdalar fiber-labelling in the caudate nucleus was not restricted to the striosomes but began to include the intervening matrix tissue. This is illustrated for case CRAm-10 in Figure 4-3C. A different trend, however, was apparent in the putamen as a district largely free of amygdalar fibers was introduced in the ventral part of the nucleus. This fiber-poor region stretched from the middle of the putamen down into the lateral central nucleus of the amygdala (Ragsdale and Graybiel, 1987). With caudal progression from this level, the label-poor district of the lateral caudate nucleus was eclipsed; fiber-labelling nearly filled the full cross-sectional area of the caudal body of the caudate nucleus and was present in the medial part of the tail. In the posterior putamen, a zone of dense labelling appeared ventromedially and near the caudal pole of the nucleus there was moderate labelling at its medial and lateral borders and weak labelling throughout.

The only compelling exception to the observation that amygdala fibers 'fill' striosomes was observed in the dorsal part of caudal putamen. As illustrated in Figure 4-3C, a zone weak in AChE staining could be distinguished in the cap of the nucleus and this zone had a precise grain-poor correspondent in the serially adjoining section. Remarkably, in several other of our cases such an 'avoid' could be seen in virtually the same location, and in case CRAm-4 the correspondence could be followed from dorsal putamen to the lateral margin of the caudate nucleus. With the possible exception of one candidate-avoid detected in case CRAm-2L in the rostral body of the caudate nucleus (and some reductions in fiber-labelling in AChE-weak zones near the base of the caudate nucleus in what we suspect is a parastriatal division of the bed nucleus of the stria terminalis (Graybiel and Ragsdale, 1983; Ragsdale and Graybiel, 1987)), we could establish no other clear-cut departures from the rule that basolateral amygdalar fibers innervate

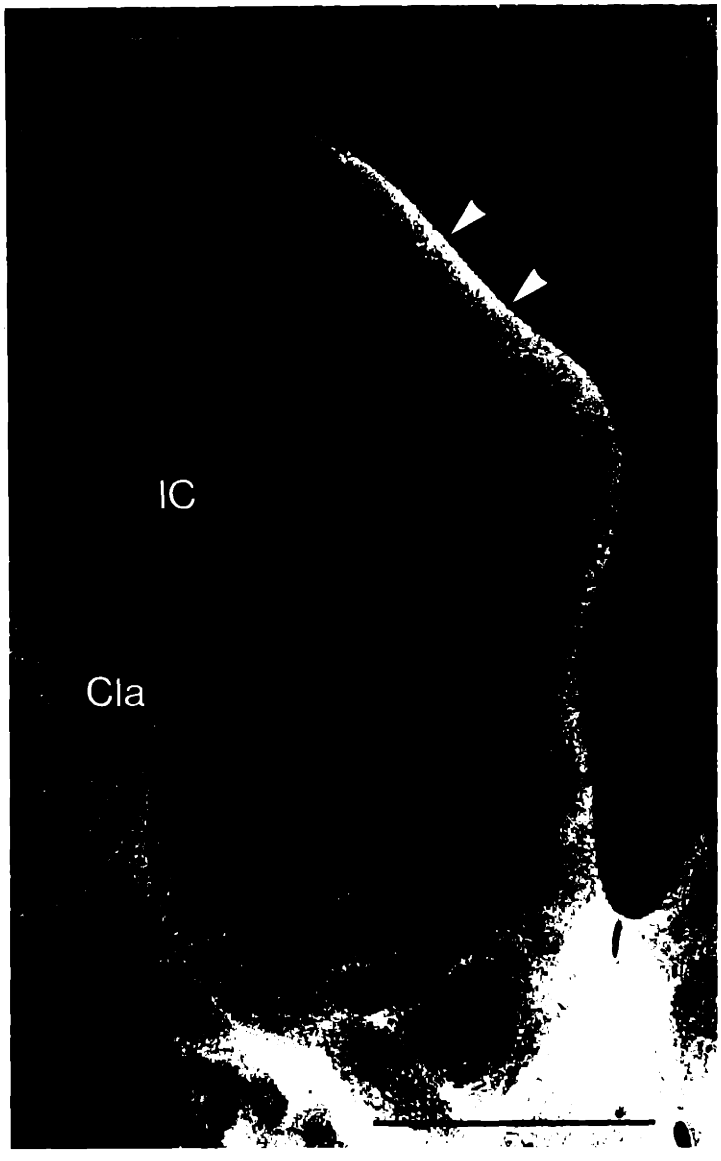
AChE-poor striosomes in their striatal field of termination. Because the AChE stain is least reliable in demonstrating histochemical inhomogeneities at caudal levels of the striatum, there may be more exceptions than we could detect.

In neither CRAm-10 nor any other case did we see more than very sparse labelling of the contralateral forebrain and even this was largely restricted to the anterior commissure and the bed nucleus of the stria terminalis.

Additional cases. Deposits were situated in the posterior part of the basolateral nucleus in three experiments. Figure 4-2 illustrates the injection site for one of these cases, CRAm-2L. In this animal an injection of ^{3}H-leucine spanned the border between the dorsomedial part of the posterior basolateral nucleus and the medial nucleus of the amygdala and included adjoining parts of the basomedial nucleus, the central nucleus and the amygdalohippocampal (transition) area. As Figure 4-4 illustrates, the resulting fiber-labelling in the striatum was mainly within a periventricular strip of tissue that spanned almost the full face of the caudate nucleus, avoiding only a dorsal quarter of the strip near the anterior end of the nucleus. At posterior levels some patches of fibers could be seen within the ventral part of the caudate nucleus and these precisely corresponded to AChE-poor striosomes detected there. In the caudal head of the nucleus the labelling was more widely distributed. A similar patterning was observed in the other cases with posterior basolateral nucleus injections, the main difference being that the medial strip was not of such even thickness as that seen in case CRAm-2L.

In case CRAm-9 a deposit of ^{35}S-methionine was centered in the anterior pole of the basolateral nucleus and involved tissue of the anterior amygdaloid area and adjacent parts of the central, lateral and basomedial nuclei (Fig. 4-2). In the caudate nucleus (not illustrated), labelled fibers were mainly restricted to the ventral half of the nucleus and though they did reach its medial edge they did not

Figure 4-4: Labelling of periventricular caudate nucleus (two arrowheads) seen after injection of caudal basolateral nucleus (case CRAM-2L). Scale bar marks 2mm.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produce labelling of a medial strip comparable to that seen in cases CRAm-2L or CRAm-10. At rostral levels of the striatum, serial section comparisons indicated a fairly precise correspondence between the grain-dense figures and the AChE-poor zones. At more caudal levels the fiber-labelling was more intense and presented a more irregular pattern of selective, but not exclusive, affiliation with the striosomes.

A much more complicated arrangement of matrix labelling was observed in case CRAm-4 (Fig. 4-5). In this experiment the ^{35}S-methionine injection site was centered in the ventral half of the anterior basolateral nucleus, in what might be called the 'pedicle' of the nucleus, and strongly involved the adjoining lateral and basomedial nuclei (see Fig. 4-2). The resulting fiber-labelling was restricted to the ventral caudate nucleus and, as illustrated in Figure 4-5A, showed a remarkable arrangement of fiber-poor zones. These 'holes' in the grain-pattern did not correspond to the AChE-poor striosomes but rather lay in the AChE-rich matrix tissue (Fig. 4-5B). The striosomes were labelled though not precisely 'filled'. This arrangement was observed throughout the caudate nucleus in this case and was also present, but to a lesser extent, in case CRAm-6. The inhomogeneities in the fiber-patterning in extrastriosomal matrix, particularly the fiber-poor zones, could not be accounted for by variations in the levels of AChE staining, but in all instances the amygdalar fibers innervated the AChE-poor striosomes.

Ventral striatal labelling. In all cases the labelling in the olfactory tubercle and nucleus accumbens was dense and extremely heterogeneous, but did not always observe compartmental tissue arrangements visible with Nissl and histochemical staining methods. A full documentation of the compartmental structuring present in the cat's ventral striatum will not be presented here (see Chapter 2), but a brief report will be made of those components selectively labelled by amygdalar fibers.

Figure 4-5: Relation between fiber-labelling (A) and AChE staining (B) observed in case CRAm-4. Arrow in A points to grain-poor 'holes' seen in the autoradiography; below the line of the arrows (A,B), labelled fibers overlie, but do not exclusively innervate, AChE-poor striosomes. The ventral division of the nucleus accumbens (dorsal border marked by arrowheads) is densely labelled except for its AChE-rich dorsomedial segment. Scale bar marks 2mm.

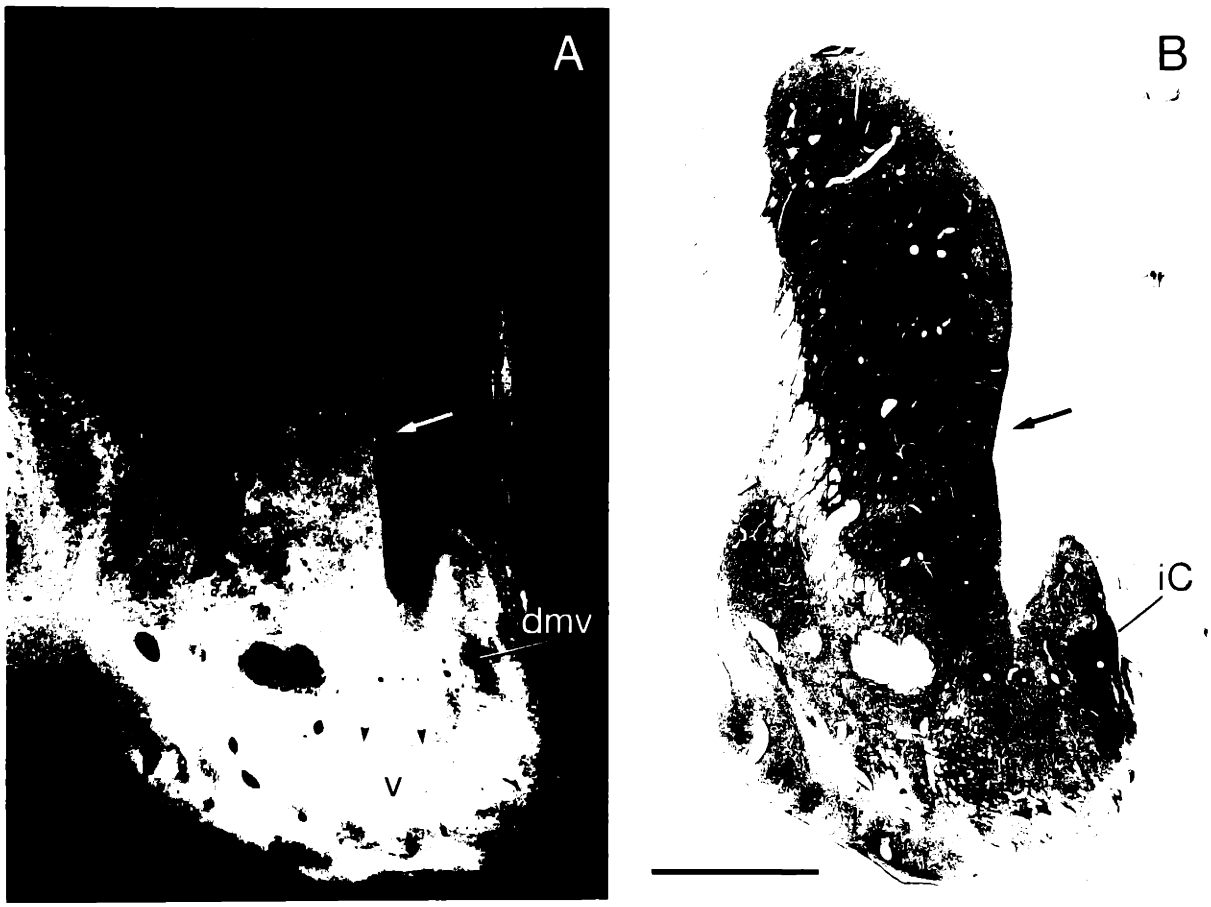
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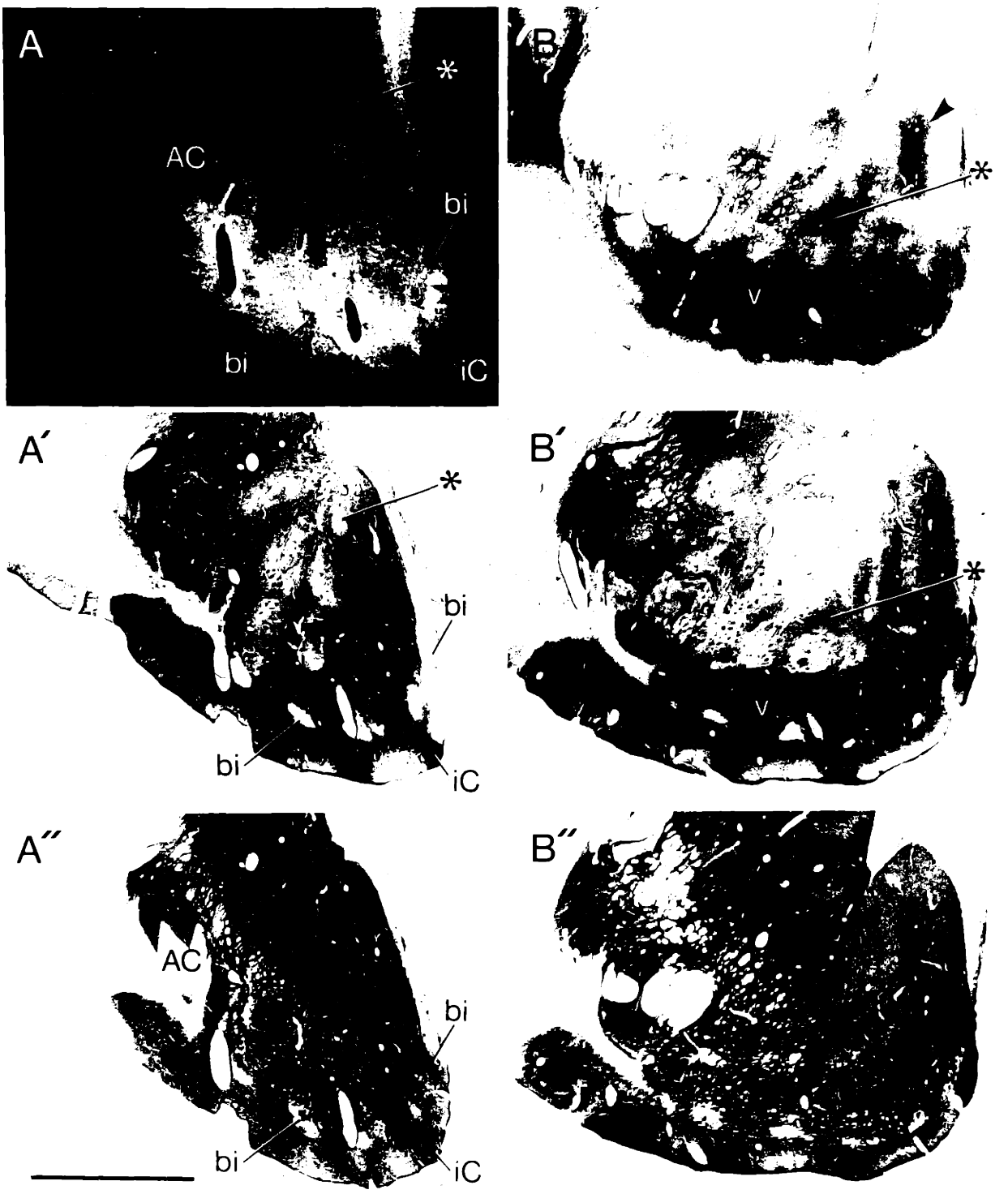
Figure 4-6: Pattern of fiber-labelling seen in rostral nucleus accumbens following injections of basolateral amygdala. Serially adjoining sections shown on left (case CRAm-4) are rostral to those depicted on right (case CHAm-1). Tissue was treated to demonstrate labelled fibers (top: A, autoradiography; B, TMB histochemistry) and BuChE (middle) and AChE (bottom) staining patterns (actual anatomical order: A,A'',A'; B',B,B''). Asterisks indicate coincidence of fiber-dense figures with BuChE-rich zones in the dorsal division of the nucleus accumbens. To ease the comparison of A and A', fiber-poor and BuChE-poor zones are marked. No comparable inhomogeneities are visible in the AChE material in these examples. Arrowheads in B indicate a different correlation obtains in the septal division of the nucleus accumbens in this case (labelled figure is AChE-rich and BuChE-poor). The BuChE-negative, AChE-positive border islands noted in A-A'' are somewhat reduced in fiber-labelling. Scale bar marks 2mm.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For the nucleus accumbens we have distinguished three divisions (dorsal, ventral and septal) (Ragsdale and Graybiel, 1987). All three are reached by amygdalar fibers. The ventral division rests at the base of the nucleus above the olfactory tubercle and is distinguished by an enhanced level of cholinesterase staining (see Fig. 4-6B). It received a moderate to heavy projection from the amygdala which rostrally was strongest in the ventral half of the division and along its dorsal border (see Fig. 4-3A) and farther caudolaterally was heavy throughout (see Fig. 4-5). There were inhomogeneities in both the fiber-labelling and the staining for enzymatic activity in this division; though these were sometimes related, no reliable correlative patterns emerged.

The dorsal division encompasses all accumbens tissue ventrolateral to the fundus of the lateral ventricle that is not included in the ventral division. The most striking finding for the nucleus accumbens was that, in the rostral part of the dorsal division, amygdalar fibers accumulated in dense pockets that coincided with zones rich in butyrylcholinesterase (BuChE) activity (Fig. 4-6A,B). We suspect that these compartments are, in essence, striosomes because when AChE-poor patches can be detected in this region, they match in position and shape the BuChE-dense figures.

The septal division is situated in the rostral part of the 'septal hook' of the nucleus accumbens; caudally it is replaced by a dorsomedial extension of the ventral division. The fiber-labelling of the septal division was remarkable in two respects. First, although there are several forms of histochemical inhomogeneity in this region, these variations were not particularly respected by the fiber-patternings (Fig. 4-6B illustrates one of the few exceptions to this observation). For example, the septal division contains small, circumscribed zones reduced in AChE activity (Ragsdale and Graybiel, 1987) and although labelled fibers in several cases did

collect over these zones, in most brains no relation between the grain-patternings and these septal zones was apparent. Second, the overall density of fiber-labelling tended to be less in this medial region of the nucleus accumbens than in more lateral districts. This reduction was more apparent caudally, where typically not just the septal division but also the dorsomedial segment of the ventral division was excluded from the zone of heavy labelling. For example, in cases CRAm-2L and CRAm-4, the labelling in the caudomedial nucleus accumbens was modest compared with that seen elsewhere in the ventral striatum and, in cases CRAm-9 and CRAm-10, this district was virtually fiber-free (see Fig. 4-3B). The only case in which there was heavy labelling of this caudomedial zone was case CRAm-11. The injection site in this experiment was centered in the dorsomedial basolateral nucleus somewhat caudal to the placement in case CRAm-2L; however, there was spread of label to the hippocampal formation and it seems likely that this was the source of the strong projection (cf. Krettek and Price, 1978a; Groenewegen et al., 1982).

As illustrated in Figure 4-6A, the ventral and medial edges of the nucleus accumbens feature small, circumscribed zones very weak in BuChE staining. Correlative studies indicate that these zones correspond to islands of cells and are fairly rich in AChE activity. Due to their appearance and location we call these zones border islands of the nucleus accumbens (Ragsdale and Graybiel, 1987). The border islands typically exhibited light to moderate grain-densities in our amygdalar cases, but it was not unusual for the border islands along the rostral and medial edge of the accumbens to be densely labelled and for those along the ventral border to be very lightly labelled or even avoided. These variations were seen both within and across the cases and were not associated in any clear way with differences across the cases in the positioning of injection sites. The large

medial island of Calleja, which adjoins the border between the septal and ventral divisions of the nucleus accumbens, was partially invaded by fibers in one case but was otherwise largely unlabelled (see Fig. 4-5).

The labelling of the olfactory tubercle in our cases was straightforward and quite similar to that reported by Krettek and Price (1978a). The olfactory tubercle consists of three layers; a molecular layer at the ventral surface of the brain and deep to this pyramidal and subpyramidal cellular layers. In the cat the pyramidal layer shows regularly spaced deflections towards the pial surface which coincide with a marked change in its cytology; the pyramidal cells are replaced by granule cell islands of Calleja (Fox, 1940). We follow Meyer and Wahle (1986) in referring to the vertical chunks of olfactory tubercle tissue covered by the islands of Calleja as the cap zones and the residual, more orthodox parts as the cortical zones. In the cortical zones, fiber-labelling was dense in the two cellular layers and in the dorsal, or deep, half of the molecular layer. The cap zones, including the islands of Calleja, were with few exceptions free of label (Fig. 4-6A). This fiber-free zone included the hilus formed deep to the islands of Calleja, which exhibits some but not all of the features of pallidal tissue (Ragsdale and Graybiel, 1987). In the fibrocellular stratum dorsal to the olfactory tubercle there was a dense accumulation of fibers, particularly over the striatal cell bridges (Heimer and Wilson, 1975), and a light to moderate accumulation over rostro-ventral extensions of the ventral pallidum as defined histochemically (Switzer et al., 1982).

Discussion

Findings on the compartmental organization of the amygdalostriatal projection

We have established by anterograde tracing techniques that in cat, as in rat and monkey (Kelley et al., 1982; Russchen et al., 1985), fibers from basolateral

amygdala do not restrict their distribution to ventral striatum, but have major excursions into dorsal striatum. Our central novel finding, established with two independent methods, is that fibers from the basolateral nucleus of the amygdala innervate AChE-poor striosomes in the caudate nucleus and BuChE-rich zones in the dorsal division of the nucleus accumbens. These, though, were not the only pattern of amygdalostriatal innervation observed. In a number of the cases there was a clear avoidance of an AChE-poor striosome in the dorsal part of the caudal putamen, in a few of the cases there was considerable labelling of the extrastriosomal matrix, and in every case there was strong inhomogeneous fiber-labelling in the nucleus accumbens which, outside an anterodorsal part of the nucleus, could not be consistently predicted by any histochemical compartmentalization.

Case CRAm-4 was particularly notable in this regard as its labelled projection to the ventral caudate nucleus not only reached the matrix, but did so in a strongly heterogeneous manner that could not be reconstructed by simply permitting fiber-bridges to connect the striosomal fiber-patches (cf. 'holes' in Fig. 4-5). These observations suggest a mosaicism for this ventral matrix region reminiscent of that recently described for the dorsolateral, somatosensory-recipient matrix of the caudate nucleus (Malach and Graybiel, 1986). A similar marriage of striosomes and parts of matrix tissue for this region has been suggested in the development of the mesostriatal dopamine projection: tyrosine hydroxylase-positive bands in ventral caudate nucleus of the perinatal cat overlie, but do not coincide precisely with, striosomes identified by thymidine autoradiography (Graybiel, 1984).

As the findings in other cases, especially case CRAm-10, were clear in establishing that parts of the amygdala do project selectively to striosomes, this

evidence that deposits not placed in the dorsal part of the basolateral nucleus, but situated elsewhere in the amygdaloid complex, produce at least collateral matrix labelling, raises the possibility that there is more than one amygdalostriatal system. Such a situation is plausible as the constituent nuclei of the amygdala are each quite distinct from one another not only in their cytology and chemistry but also in their neural projections (Krettek and Price, 1978a; Hall, 1972; Price, 1981b; de Olmos and Ingram, 1972): it is the central nucleus that provides the broad sweep of subcortical efferent connections stretching from basal forebrain at least as far as the lower medulla; the medially situated nuclei including the medial and basomedial nuclei that project to the ventromedial nucleus of the hypothalamus; and the basolateral complex (lateral, basolateral and basomedial nuclei) that projects to the neocortex. Closer inspection of each of these amygdalofugal systems discloses further specificity in their organization. For example, projections to the frontal cortex are more favored by the basolateral nucleus than by the lateral nucleus.

Consistent with this high degree of ordering, data from retrograde axonal transport experiments in rat and cat indicate that the bulk of the amygdalostriatal projection issues from the basolateral nucleus and that a more modest contribution originates in the basomedial nucleus (Kelley et al., 1982; Veening et al., 1980; Royce, 1978a; Groenewegen et al., 1980; Jayaraman, 1985). This dual origin is of interest because the basolateral and basomedial nuclei, although adjoining elements in the basolateral complex, are not significantly linked in the internal circuitry of the amygdala (Krettek and Price, 1978a; Price and Amaral, 1981; Aggleton, 1985). For the basolateral nucleus, association connections are made mainly with itself and with the central nucleus. The basomedial nucleus, by contrast, receives a massive projection from the lateral nucleus, and both of these nuclei in turn

connect with the cortical, medial and central nuclei. This yoking of the basomedial nucleus with the lateral nucleus, and independence of the basolateral nucleus, is also strongly evident in the distribution of afferent fibers from different districts of the diencephalon (Ottersen and Ben-Ari, 1979; Turner and Herkenham, 1981; Russchen, 1982; unpublished observation; see also Fig. 4-7B,C). These observations suggest that, to the extent there are segregated trans-amygdalar channels, the striatum, in receiving input from both the basolateral and basomedial nuclei, participates in at least two of them.

It seems possible, then, that the amygdalostriatal projection is divided into a striosomal system of basolateral nucleus origin and a second, bi-compartmental (or even extrastriosomal) system originating from outside the dorsal basolateral nucleus, and possibly from the lateral nucleus-basomedial nucleus dyad. Consistent with this view is the placement of the deposit in case CRAm-4: it mainly involved the basomedial nucleus and the pedicle of the basolateral nucleus, both of which are known to project to the ventral caudate nucleus (Jayaraman, 1985). Though projections from these zones can not account for the 'putamenal avoid' noted in case CRAm-10, this fiber-labelling could have originated in the lateral nucleus as a small connection from this nucleus to a comparable region of the rat caudoputamen has been noted by Kelley et al. (1982).

Finally, the absence of systematic correspondences in most of the nucleus accumbens labelling may also have been due to injection site involvement of multiple projection-systems. These possibilities clearly deserve further study.

Comparison with previous studies of the amygdalostriatal projection

Kelley et al. (1982) in their autoradiographic study of the amygdalostriatal projection in the rat noted that fibers did not reach an antero-dorsolateral

quadrant of the caudatoputamen, and suggested that amygdalar fibers may be excluded from striatum receiving input from sensory motor cortex. Our failure in the cat to label more than scattered fibers in a zone in anterodorsal putamen and dorsolateral head of the caudate nucleus that receive fibers from motor cortex fully supports their suggestion and agrees with anterograde autoradiographic studies by Russchen et al. (1985) in the monkey. Our observations suggest further that additional striatal zones adjoining the sensory-motor-recipient sector may carry a reduced complement of fibers from the basolateral amygdala. At least one of these zones appears to receive afferent projections from area 7, which would fit nicely with a failure to date to detect amygdalar projections to parietal cortex in cat or monkey (Krettek and Price, 1977a; Macchi et al., 1978; Amaral and Price, 1984).

Not all deposits in the basolateral nucleus labelled the full sweep of amygdalar projections to dorsal striatum. In particular, the labelling elicited by injections involving the posterior basolateral nucleus was largely restricted to a strip of tissue running along the ventricular face of the caudate nucleus. These deposits also involved a dorsal part of the basomedial nucleus, but it seems unlikely that this was the source of the projection. First, Russchen and Price (1984) reported in the rat comparable labelling in medial caudatoputamen following a PHA-L injection of the posterior basolateral nucleus. Second, injections of anterograde tracers into the primate magnocellular basal accessory nucleus- a possible homologue of the cat's dorsal basomedial nucleus (Price, 1981a and unpublished observations; see Fig. 4-7A)- do not produce such periventricular labelling (data from macaque (Russchen et al., 1985) and squirrel (unpublished observations) monkeys). And third, Jayaraman (1985), working in the cat, found some labelled cells in the posterior part of the basolateral nucleus after injections of HRP-WGA along the medial face of the caudate nucleus. It should be added that

there was also some label located more centrally, in ventral and caudal caudate nucleus, in these cases and this was situated in striosomes.

Although the studies in rat and monkey did not examine the compartmental distribution of the amygdalostriatal projection, it seems likely that the basolateral nucleus in the rat and the magnocellular basal (laterobasal) nucleus in the primate would project to striosomes as their homology with the basolateral nucleus of the cat appears secure (Price, 1981a). Possible homologous sources for a matrix projection similar to that seen in case CRAm-4 are less certain. By position, the ventrally situated parvocellular basal (mediobasal) and parvocellular basal accessory nuclei of the primate are the most plausible candidates for tissue similar to the pedicle of the basolateral nucleus and adjoining basomedial nucleus (injected in cat CRAm-4). Price and coworkers (see Price, 1981b), however, have suggested that the parvocellular basal nucleus is homologous to the posterior basolateral nucleus of the cat. While there are good arguments for this view (Russchen et al., 1985), there are also arguments against it: 1) in the cat the anterior and posterior basolateral nucleus are heavily interconnected, but their postulated homologs in the monkey, the magnocellular and parvocellular divisions of the basal nucleus, are not; 2) injections of the parvocellular basal nucleus of the monkey (case DM31 of Russchen et al. (1985)) do not produce labelling of a medial strip in the caudate nucleus (see discussion in previous paragraph). Resolution of these issues can only come from direct examination of the compartmental organization of the amygdalar projection in the monkey.

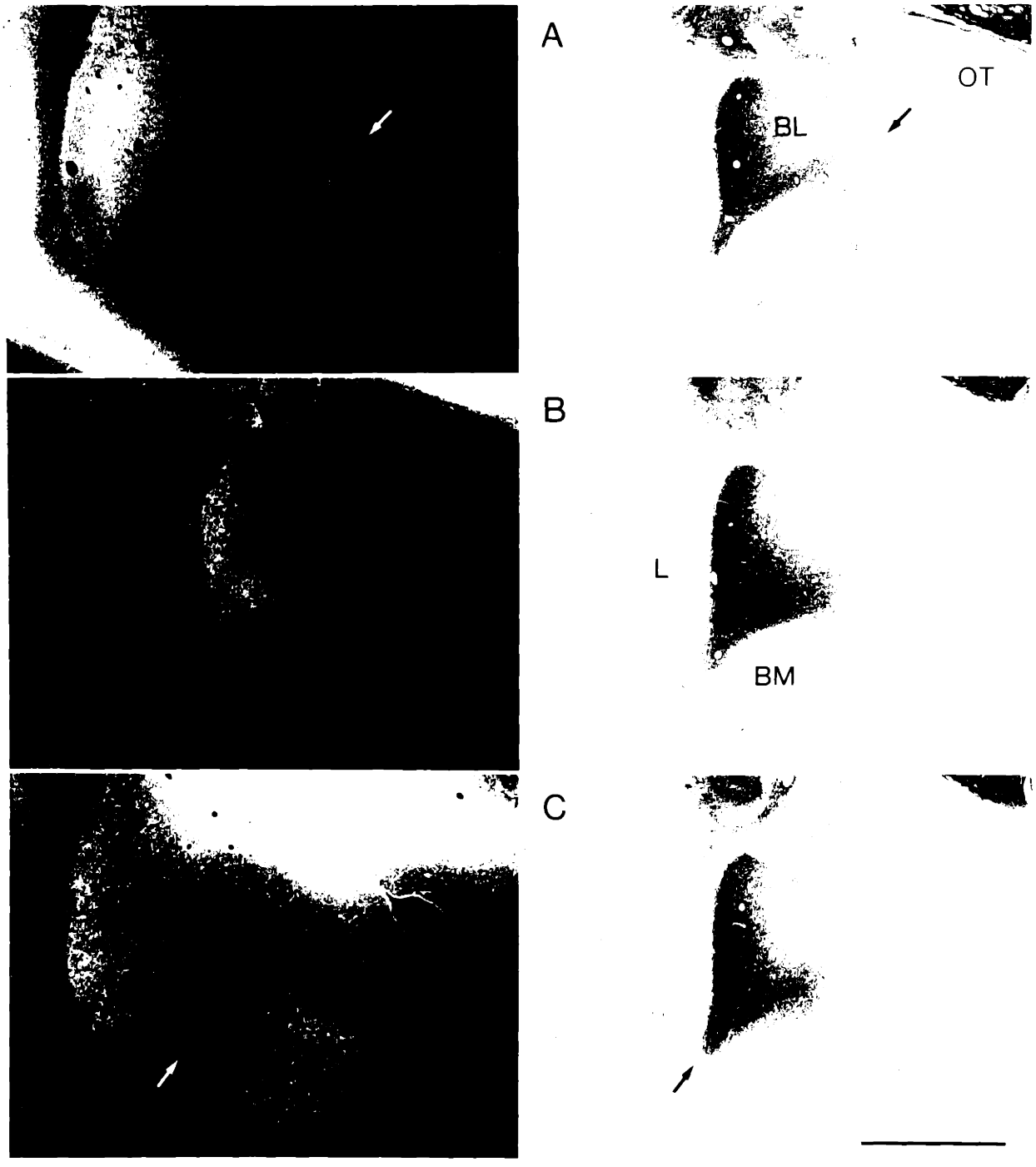
The amygdala and basal ganglia circuitry

The finding that deposits involving the dorsolateral part of the anterior basolateral nucleus give rise to the most extensive and precise labelling of striosomes raises the question of whether this part of the basolateral complex is

special in other aspects of its connections with basal ganglia circuitry. A potentially important finding from retrograde tracing experiments is that injections in the basolateral nucleus label neurons in the ventral pallidum and the dorsal substantia innominata (Russchen, 1982b; Grove et al., 1983; Carlsen et al., 1985). Light and electron microscopic studies have suggested that these neurons may receive striatal input (Zaborszky et al., 1984; Haber et al., 1985; Grove et al., 1986; Grove and Ingham, 1986). Therefore, the basolateral nucleus may be the target of a projection from striatum to ventral pallidum to amygdala.

The receipt of trans-pallidal input from the striatum may not set the basolateral nucleus apart from the lateral and basomedial nuclei: Russchen (1982) has reported that, following injections of retrograde tracers into the lateral nucleus, some cells were labelled in a posterior region of the substantia innominata which she identified as the nucleus of the ansa lenticularis. We, after a massive injection of radiolabelled amino acids into a caudal pallidal region that includes this part of the substantia innominata, observed selective transport not only to the lateral nucleus, but also to the basomedial nucleus (see Figure 4-7C). And although this part of the substantia innominata has not yet been shown to receive striatal afferents, it does exhibit some of the histochemical characteristics diagnostic of pallidal tissue, such as a neuropil rich in substance P- and met-enkephalin-like immunoreactivity (unpublished observations; Groenewegen and Russchen, 1984). If these observations are confirmed, it would suggest that the basolateral nucleus is not distinguished by receiving a transpallidal striatal system outflow, but by being linked through the ventral pallidum with parts of striatum that receive input from prefrontal cortex. By contrast, the lateral and basomedial nuclei would appear to receive, by way of projections from more caudal circum-pallidal districts, trans-striatal input from temporal cortex.

Figure 4-7: Connectional architecture of the basolateral complex of the amygdala. Left, Demonstration of tracer-substances transported to the amygdala following large deposits placed in basal forebrain and cortex. Right, Serially adjoining sections stained for AChE activity. A, TMB-processed histochemical labelling resulting from a massive deposit of HRP-WGA centered in caudal perirhinal cortex and including laterally and dorsally adjoining temporal cortex. Comparison suggests that major sources of amygdala input to temporal regions are the lateral nucleus and a dorsal portion of the basomedial nucleus contiguous with the medial basolateral nucleus. From studies in monkey on the cortical relations of the basolateral complex (Price, 1981b; Amaral and Price, 1984), this second zone appears homologous to part of the primate magnocellular basal accessory nucleus. B, Autoradiographic labelling produced by a very large injection of ^{3}H-amino acids placed into medial putamen and lateral pallidal tissue at levels where the anterior commissure sets ventral pallidum apart from globus pallidus. Fibers from the region of rostral pallidum are seen to reach the basolateral nucleus, particularly those portions densest in AChE staining. C, Autoradiographic labelling produced by a similarly large deposit of tritiated label centered in caudal pallidal tissue and including the entopeduncular nucleus, globus pallidus and a posterior substantia innominata region situated above the central nucleus. Fibers from caudal peripallidal tissue innervate ventral portions of the lateral and basomedial nuclei, a pattern largely complementary to that seen in B. Arrows in A and C added as fiducial marks. Scale bar marks 2mm.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The striosome-projecting parts of the basolateral complex may, however, be favored in the *density* of their innervation by at least cholinergic basal forebrain. Cholinergic neurons are included among the cells in the basal forebrain that project to the basolateral complex (Russchen, 1982b; Grove et al., 1983; Carlsen et al., 1985) and, according to findings in the rat (Emson et al., 1979), much of the choline acetyltransferase (ChAT) and AChE in the basolateral nucleus does come from basal forebrain. Examination of tissue taken from the basolateral nucleus and stained for AChE activity or ChAT-like immunoreactivity (Fig. 4-7A and unpublished observations) demonstrates that it is the dorsolateral part of the basolateral nucleus that is richest in these cholinergic markers; the basomedial and lateral nuclei exhibit more moderate levels of AChE activity.

The basolateral nucleus may also be distinguished from the other amygdalar districts in its distance from hippocampal targets within ventral striatum. Kelley and coworkers noted that the medial nucleus accumbens in the rat was not strongly labelled after amygdalar injections, but that it was well-labelled after deposits of tracer into the fornix (Kelley et al., 1982; Kelley and Domesick, 1982). This evidence suggested that the well-known dual input of amygdala and hippocampal formation to ventral striatum (Fox, 1943; de Olmos and Ingram, 1972; Raisman et al., 1966) might not be coordinately distributed. Our findings also indicate that the basolateral amygdalar innervation of the medial nucleus accumbens is somewhat less dense than that of more lateral districts. What is most conspicuous in our material, however, is that the caudomedial nucleus accumbens receives hardly any input from dorsal and rostral parts of the basolateral nucleus-that is, those parts that appear to project most extensively to striosomes. This caudomedial district, moreover, has been shown in the cat to receive a sizable projection from the ventral (temporal) subiculum and the amygdalohippocampal

area (Krettek and Price, 1978a; Jayaraman, 1985). Russchen et al.'s findings in the primate (1985) are similar to ours in suggesting that it is medial and ventral parts of the amygdala, and not the magnocellular basal nucleus, that project to medial nucleus accumbens. This is of particular interest as amygdalar projections to hippocampal formation appear to be much more robust in the monkey than in other species. Based on other reports from this group, it seems that these medial accumbens-projecting districts in the amygdala, and not the magnocellular basal nucleus, are also the zones with the deepest projections into hippocampal formation (Amaral, 1986).

Finally, the basolateral nucleus appears special in its relationship to the dopamine-containing system of the basal ganglia as it, and its affiliate, the central nucleus, are major amygdalar targets of the midbrain dopamine neurons (Fallon et al., 1978; Meibach and Katzman, 1981). Interestingly, these amygdalar targets appear to return this midbrain input directly, in the case of the central nucleus, and indirectly, through its projections to striosomes and the ventral striatum, in the case of the basolateral nucleus (Krettek and Price, 1978a; Hopkins et al., 1981; Price and Amaral, 1981; Gerfen, 1984; Jimenez-Castellanos and Graybiel, 1985; Nauta et al., 1978; Groenewegen and Russchen, 1984).

Functional considerations

Behavioral studies suggest that the consequences of amygdalectomy make up a related set of symptoms. In monkeys these include an increase in tameness and decrease in emotional responsiveness, "psychic blindness" and a "hypermetamorphic" impulse to action, and an increase in orality and possibly sexuality (Kluver and Bucy, 1939; Weiskrantz, 1956; Horel et al., 1975; Aggleton and Passingham, 1981). These behavioral signs have been interpreted as indicating a role for the amygdala in establishing and attributing affective qualities (including

reward contingencies) to perceived objects (Weiskrantz, 1956; Jones and Mishkin, 1972; Spiegler and Mishkin, 1981), an interpretation general enough to encompass the "sham rage" response sometimes seen after amygdalar damage in cats (Bard and Mountcastle, 1948; Kaada, 1972). A more rarefied description of this amygdala function, that it participates in the formation and rendering of those associations that underlie object identification, is indicated by the recent finding of Murray and Mishkin (1985) that damage to the amygdala compromises cross-modal associative memory mechanisms. Our interest is, naturally, in what the functions of the basolateral nucleus might be. It has, unfortunately, not proved possible to "fractionate" the syndrome with subtotal amygdala lesions (Aggleton and Passingham, 1981). Although this may be for technical reasons, such as the tremendous interconnectivity among amygdalar nuclei, it seems reasonable to suppose that the consequences of basolateral nucleus destruction would appear among the set of related dysfunctions seen after total amygdalectomy.

The functional contribution of the basolateral nucleus may, in fact, be suggested by its connections with the extrapyramidal system. The comments of Kluver and Bucy (1939) concerning the hypermetamorphosis seen in monkeys with both temporal lobes removed are instructive in this regard. Its "most impressive feature", they note, "is that the presentation of any visual object will, whenever possible, immediately lead to a motor response". It seems plausible that the motor system of these monkeys, presented with objects which it 'recognizes' (in the limited sense outlined by Gaffan (1974) and Mishkin and Delacour (1975)) but can no longer identify, reasonably enough initiates an exploration of these objects. In this speculation, the excessive exploratory behavior would be a consequence of disconnection of the amygdala, but not the rest of the apparatus of perception, from the basal ganglia. One role of amygdaloid input would be to temper these

responses, directing them only to novel and apparently safe objects of possible interest. Though the projection from the basolateral nucleus to ventral striatum and ventromedial striosomes is only one of several direct and indirect connections between these systems (Krettek and Price, 1978a; Price and Amaral, 1981; Nauta and Domesick, 1978; Grove, 1987), its prominence suggests that it may play an important part in such modulation of perceptuo-motor responses.

The basolateral nucleus and the anatomy of input to striosomes

The anatomical implications of a strong affiliation of the basolateral nucleus of the amygdala for striosomes of the ventral and medial caudate nucleus are more sure. One implication bears on the difficulty in searching for affinities across districts of the striatum given the poverty of long-distance internal connections within the striatum. An alternative approach to this problem may be to link striatal zones on the basis of shared afferent or efferent connections. The finding in this study, that the basolateral nucleus picks out parts of the ventral striatum and striosomes of the ventral and medial caudate nucleus, presents one such linkage, one that may be further supported by studies of striatal efferent connections suggesting that medial striosomes and the nucleus accumbens may share midbrain targets, such as the pars compacta of the substantia nigra (Gerfen, 1984; Jimenez-Castellanos and Graybiel, 1985; Nauta et al., 1978). It will be interesting to see how these affinities fare in the examination of the anatomy of other striatal afferent projections.

A second implication of this work concerns the suggestion of a distinction in limbic cortical circuitry between medial cortical regions linked to the anterior nuclei of the thalamus and frontal and rostral temporal regions linked to the amygdala. We have found (see Chapter 6) that most of the cortex of the cingulate region, in its projection to medial and ventral caudate nucleus, innervates matrix

tissue whereas most of amygdala-afferented cortex (including frontal and temporal regions) projects to striosomes in at least a part of its striatal region of termination. At least at this first stage of basal ganglia processing, then, these subdivisions of the limbic system reach the same striatal district but are kept separate by compartmentation mechanisms.

A third implication of the findings of this study is that a basolateral nucleus-to-striosome projection, though not massive, may be a direct reflection of a relationship seen more strongly in indirect circuits. We base this suggestion on the corticostriatal data just mentioned and, in particular, on our findings on the thalamostriatal system (see Chapter 5). In brief, these are that the main sources for thalamic projections that reach striosomes are the midline nuclei, which are the same regions of dorsal thalamus that project to the amygdala.

The basolateral nucleus of the amygdala does not innervate all striosomes. From the findings reviewed here, though, it is tempting to conclude that a strong association with the basolateral nucleus predicts a selective affiliation with the striosomal compartment. For several reasons this conclusion would be premature. First, there are regions of cortex that sharply complicate this view, such as the anterior limbic area in the cat, which is strongly and selectively reciprocally connected with the basolateral nucleus of the amygdala but which does not innervate striosomes. Second, though the basolateral nucleus projects to many regions of cortex that in turn project to striosomes, these cortical regions do not innervate striosomes everywhere in their striatal district of termination but often avoid them, even in the same striatal districts where basolateral nucleus fibers fill them. Clearly then, if there is a coherence to the organization of input to striosomes across striatum, it is not a simple one of identical innervation or even one of related afferent structures showing equivalent innervation, but must at the

least be a complex one reflecting the circuitous and hierarchical features of forebrain anatomical organization.

Chapter 5

The Thalamostriatal Connection

For students of brain organization, the anatomy of the dorsal thalamus has always had a special appeal. Some of this appeal is clearly due to a curiosity about the thalamus as a necessary relay for much of the information passing to the telencephalon. But, at least for anatomists, a part of this appeal lies in the highly ordered arrangement of efferent connections that the thalamus impresses upon its inputs. Some aspects of this orderliness are transparent: thalamic projections are essentially ipsilateral and almost exclusively ascending ones (Jones, 1985). Other aspects are less clear, but, for the thalamocortical system, apparently include restrictions on the areal and laminar targets of individual thalamic nuclei: for example, the layers of termination of given thalamic nuclei appear particularized from possibly as and there appears to be a global topography to much of the projection to cortex whereby adjoining, cross-nuclear slabs of thalamus are reciprocally connected with adjoining regions of cortex (Waller, 1934; Lashley, 1941; Kievit and Kuypers, 1977). An overall scheme of thalamic efferent connections will need not only to reconcile these, and other (Macchi, 1983), restrictions on cortical relations, but also to incorporate an account of thalamic projections to subcortical forebrain targets, including the amygdala and the striatum.

The thalamostriatal projection, unlike the thalamocortical system, does not issue from all dorsal thalamic nuclei. Classic studies employing the method of retrograde degeneration established that its chief sources are the anterior intralaminar (central medial, paracentral and central lateral nuclei) and posterior

intralaminar (centromedian and parafascicular nuclei) nuclear complexes (Droogleever-Fortuyn and Stephans, 1951: Cowan and Powell, 1955; Powell and Cowan, 1954, 1956). Modern retrograde transport studies corroborated this judgment and confirmed additional thalamostriatal projections from the paratenial, paraventricular and rhomboid nuclei of the midline, from parts of the rostral ventral nuclear complex including the ventroanterior nucleus, and from posterior association nuclei (Jones and Leavitt, 1974; Royce, 1978b; Sato et al., 1979; Macchi et al., 1984; Beckstead, 1984a; Jayaraman, 1985). These reports also documented a spatial organization to the projection. Studies based on degeneration techniques indicated, for example, that the centromedian nucleus connects mainly with the putamen and the paratenial nucleus, selectively with the nucleus accumbens (Le Gros Clark and Russell, 1939; Cowan and Powell, 1955; Powell and Cowan, 1956). In the most comprehensive modern treatment of the matter, Beckstead (1984a) suggested that there are two thalamostriatal systems: a rostral one arranged as a ring around the mediodorsal nucleus and composed of the anterior intralaminar nuclei plus the rhomboid and paraventricular nuclei of the midline; and a posterior one corresponding to the posterior intralaminar complex. Each system projects topographically to the entire striatum, preserving mediolateral and dorsoventral axes in the connection. By this account the thalamostriatal projection, in exhibiting a global, supra-nuclear topography, appears similar to the thalamocortical system.

Detailed study of the distribution of thalamic fibers within the striatum became possible with the development of modern anterograde transport tracing methods. Initial reports employing the autoradiographic technique showed that thalamostriatal fibers are inhomogeneously distributed within their fields of termination (Kalil, 1978; Royce, 1978a; Herkenham, 1978a). This was in line with findings of 'patchy' distributions for other striatal inputs, including those from the

cortex, the substantia nigra and the amygdala (Kunzle, 1975; Wright and Arbuthnott, 1981; Kelley et al., 1982) and it is now well-established that most of these fiber-patternings are due to an inhomogeneous structuring to the striatum itself (Ragsdale and Graybiel, 1981, 1984; Moon Edley and Herkenham, 1984; Donoghue and Herkenham, 1986; Jimenez-Castellanos and Graybiel, 1987). By histochemical analysis, the striatum consists of two compartments, striosomes and matrix, arranged so that in tissue cross-sections the striosomes appear as half-mm wide zones regularly distributed throughout a matrix tissue of different chemical composition (see Chapter 2). This finding of compartmental structure in the striatum, coupled with evidence for an inhomogeneous distribution for most thalamostriatal projections (Beckstead, 1984a), raised the possibility that, just as there are thalamocortical systems distinguished according to their lamination patterns, there might be distinct thalamostriatal systems distinguished according to their compartmental targets.

In 1981 Herkenham and Pert examined the distribution of fibers originating in the parafascicular nucleus of the rat thalamus and demonstrated that these fibers avoid striatal compartments rich in opiate binding sites and weak in AChE activity. This finding has been interpreted as indicating that the thalamus does not project to the striosomes (Donoghue and Herkenham, 1986). We found such a conclusion puzzling as it predicted that the presence of athalamic zones within the striatum and suggested that the thalamus, in reaching only one of the striatal compartments, should be classed with the amygdala, which predominantly innervates the striosomes, rather than with the cortex, which reaches both compartments. The results of our investigation demonstrate that parts of thalamus do project to striosomes and that there is no reason to expect athalamic zones in the cat's striatum. They also argue for a reinterpretation of the findings of modern

retrograde tracing studies on thalamostriatal topography. Finally, when viewed synoptically, the observations allow a fundamental parcellation of the thalamostriatal connection into medial and lateral divisions distinguished according to their compartmental targets within the striatum.

Results

The compartmental organization of the thalamostriatal projection was explored by making large deposits of anterograde tracers, principally radiolabelled amino acids, throughout the thalamus. We chose to make the deposits large so that the density of labelling in the striatum would be sufficient to permit informative comparisons between the patterns of labelled fibers and the arrangement of the histochemically defined striatal compartments. As a consequence, the injection sites in nearly every experiment implicated more than one, and usually several, thalamic nuclei as identified in standard accounts (Berman and Jones, 1982; Ingram et al., 1932). In spite of the interpretive limitations of such data, the central results of this study are clear. First, as documented below, parts of dorsal thalamus do project to striosomes. Second, as is apparent from examining chartings of the injection sites compiled according to the compartmental target of their striatal connections, medial thalamic deposits (Fig. 5-1) elicit labelling of striosomes while lateral thalamic deposits (Fig. 5-4) primarily produce labelling of the matrix.

Identification of thalamic nuclei that project to the striatum

Because thalamostriatal connections have been frequently (Jones and Leavitt, 1974; Royce, 1978b; Sato et al., 1979; Macchi et al., 1984) and comprehensively (Beckstead, 1984a; Jayaraman, 1985) studied in the cat with retrograde tracing methods, provisional identification of nuclei participating in the medial and lateral systems was to some extent possible. Consequently, in describing our injection sites,

we highlight those nuclei known to project to the striatum. In most instances we follow the atlases of Ingram et al. (1932) and Berman and Jones (1982) in identifying thalamic nuclei, but because of the size of our deposits, we chose, where appropriate, the coarser of parcellations of thalamus. For example, the paraventricular nucleus of the thalamus is composed of cytologically distinguished medial and lateral division, which are sometimes called anterior and posterior divisions (Berman and Jones, 1982). We do not refer to these divisions as our deposits could not possibly distinguish them. For this same reason, we follow Berman and Jones (1982) in referring to the midline thalamus between the paraventricular and central medial nuclei as the rhomboid nucleus and in not distinguishing possible constituent nuclei, such as the intermediodorsal nucleus.

Nuclei of the midline and of the rostral intralaminar group. The paraventricular and rhomboid nuclei, and to an extent the paratenial nucleus, are the midline nuclei that contribute to the ring of striatally projecting neurons arranged around the mediodorsal nucleus (Beckstead, 1984a). The central lateral, paracentral and central medial nuclei of the rostral intralaminar group form its lateral (and ventral) constituents. This ring is not distinguished as a coherent structure in cytological preparations even though it can be recognized, in retrograde transport studies, as a principal source of striatal projections and, apparently, in anterograde experiments, as an interstitial nuclear complex for ascending projections from brainstem (Edwards and de Olmos, 1976; Royce and Mourey, 1985). The dorsal arc of this ring, which links the central lateral nucleus with the paraventricular nucleus, is particularly difficult to delineate, but it may correspond, at least in part, to the central dorsal nucleus of Niimi and Kuwahara (1973) (see Jayaraman (1985)). Caudally, though, these dorsally situated cells sometimes appear confluent with labelled neurons that clearly reside in lateral

posterior thalamic nuclei (Beckstead, 1984a). Because our injections do not separate these elements, we follow Beckstead (1984) and refer to this district as the parastria medullaris zone.

Nuclei of the posterior intralaminar group. We relied on the heavy staining of the centromedian-parafascicular (CM-Pf) nuclear complex in material prepared for AChE histochemistry to distinguish it from adjoining diencephalon (Graybiel and Berson, 1980). In an attempt to validate this reliance, we compared the profile of the complex as it appears in AChE staining with the distribution of fibers labelled by a massive injection of the entopeduncular nucleus (cf. Mehler, 1966; Nauta, 1979). Figure There is a precise correspondence between the fiber-labelling and the histochemistry. We did not attempt to distinguish a centromedian from a parafascicular nucleus although this is sometimes done in the cat (Niimi and Kuwahara, 1973; Berman and Jones, 1982). We were, however, able to recognize a centromedian-type territory in the complex based on its receipt of fibers from pericruciate cortex and its select projections to the sensory motor-recipient sector of the striatum (see below).

Deposits involving the rostral pole of the thalamus

Deposits of radiolabelled amino acids were centered near the rostral limits of the thalamus in two cases. In case CHRT-1 (Fig. 5-1:A-C), the injection site occupied the rostral end of the paraventricular and paratenial nuclei and extended anteriorly into the medial division of the bed nucleus of the stria terminalis and posteriorly as far as the anterior ends of the rhomboid nucleus and nucleus reuniens. The labelling elicited in dorsal striatum was very weak and completely confined to the most ventromedial part of the rostral caudate nucleus. By contrast, the medial nucleus accumbens exclusive of a rostromedial part of its septal division was densely labelled. This labelling was especially prominent in the caudal half of

the nucleus. The deposit in case CLRT-1L (Fig. 5-1:A-C) was lateral to that of CHRT-1, largely sparing the paraventricular nucleus and involving the rostral end of the ventroanterior nucleus. The labelling in the nucleus accumbens was similar to that seen in CHRT-1; there was in addition light labelling medially in the caudate nucleus which could not be scored with respect to the histochemical compartments.

Cases that primarily produced labelling of striosomes

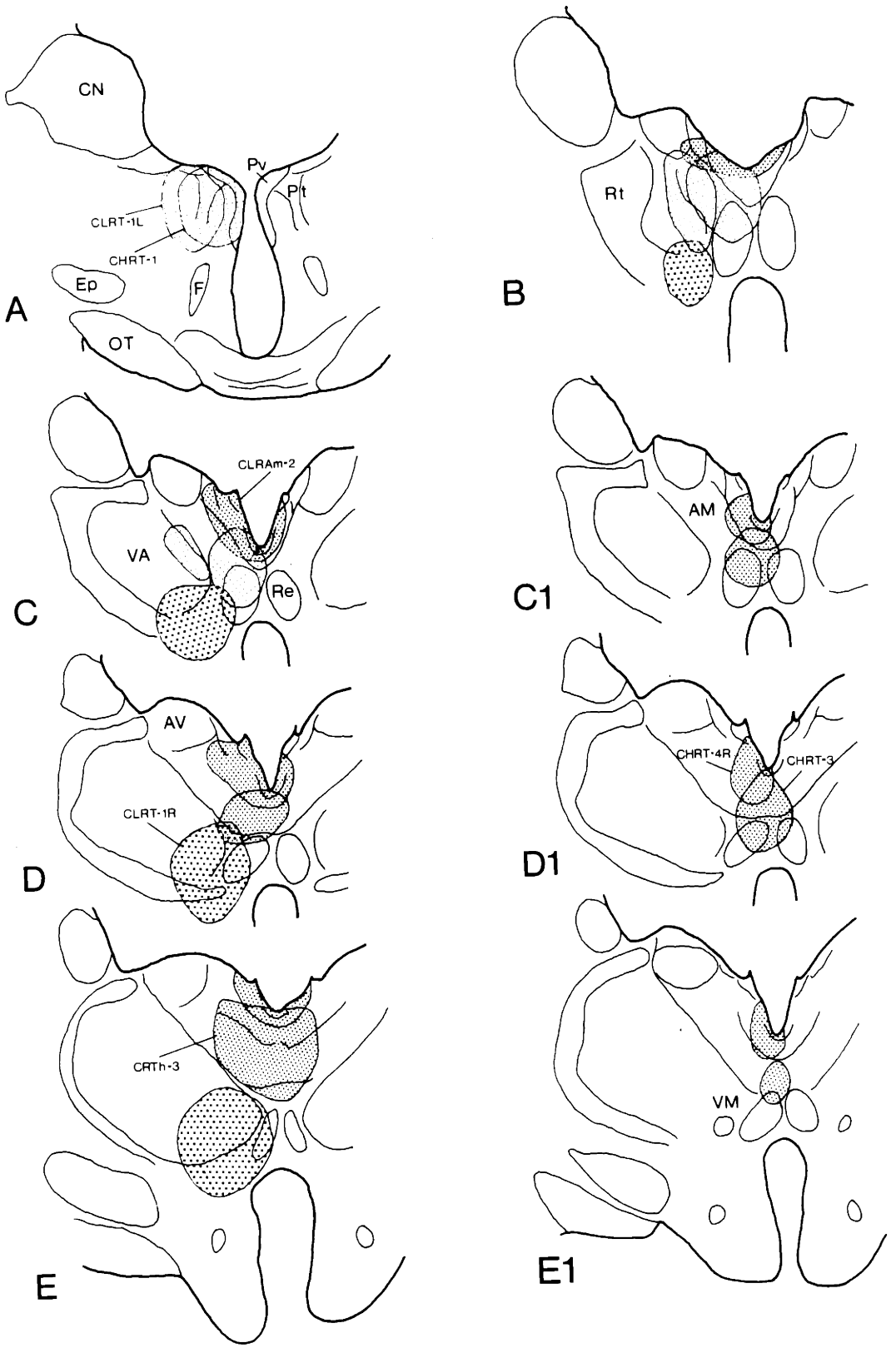
Anterograde tracer deposits that involved the rhomboid nucleus or the paraventricular nucleus (with the apparent exception of its rostral pole) resulted in strong labelling of striosomes in dorsal striatum.

Deposits involving the rostral paraventricular and rhomboid nuclei. In three cases, injection sites centered in midline thalamus rostral to the appearance of the intralaminar nuclei produced significant labelling in dorsal striatum. Two of these sites mainly involved the paraventricular nucleus (CLRAm-2, Fig. 5-1:B-G; CHRT-4R, Fig. 5-1:C1-E1); the deposit in the third was situated at the anterior end of the rhomboid nucleus (CHRT-3, Fig. 5-1:C1-E1). The pattern of labelling was similar in the three cases. As illustrated for case CHRT-4R (Fig. 5-2A), labelled fibers accumulated along the ventricular edge of the caudate nucleus, often extending three-quarters of the distance up its face. Stretching away from this medial strip of labelling were circumscribed patches of labelled fibers. Comparison of the autoradiograms and serially adjoining, AChE-stained sections established that the labelled patches precisely matched AChE-poor striosomes (Fig. 5-2A). At the base of the caudate nucleus, labelled striosomes were present laterally as well as medially and there was modest labelling of the intercalated matrix tissue. Fiber-labelling was broadly distributed in the ventral striatum and particularly dense in the medial nucleus accumbens, especially caudally.

Abbreviations

AM	Anteromedial nucleus
AV	Anteroventral nucleus
CeM	Central medial nucleus
CG	Central gray substance
CL	Central lateral nucleus
CM	Centromedian nucleus
CN	Caudate nucleus
Ep	Entopeduncular nucleus
F	Fornix
FR	Fasciculus retroflexus
Hb	Habenular complex
IC	Internal capsule
LD	Lateral dorsal nucleus
LG	Lateral geniculate body
LIo	Lateral intermediate nucleus, oral division
LM	Lateral medial nucleus
LPm	Lateral posterior nucleus, medial division
MD	Mediodorsal nucleus
MG	Medial geniculate body
M	Mammillothalamic tract
NA	Nucleus accumbens
OT	Optic tract
PC	Paracentral nucleus
Pf	Parafascicular nucleus
Pt	Paratenial nucleus
Pul	Pulvinar
Pv	Paraventricular nucleus of the thalamus
Rt	Reticular nucleus of the thalamus
Re	Nucleus reuniens
Rh	Rhomboid nucleus
Sg	Suprageniculate nucleus
VA	Ventroanterior nucleus
VB	Ventrobasal complex
VM	Ventromedial nucleus
VL	Ventrolateral nucleus

Figure 5-1: Chartings of the medial thalamic injection sites. Regularly spaced transverse sections are arranged in rostral to caudal sequence and ordered alphabetically. To ease reading of the illustrations where multiple overlapping deposits occur, selected runs of sections are duplicated (C1,D1,E1 match C,D,E, respectively). The cases that elicited selective labelling of striosomes are highlighted by a stipple of dots of moderate density. The injection site of the exceptional case CLRT-1R is indicated by a stipple of large dots and the two deposits involving the rostral pole of the thalamus, which led to labelling principally in the nucleus accumbens, are noted by a stipple of light density. The control injection CRTh-13L is illustrated by dark shading of irregular texture.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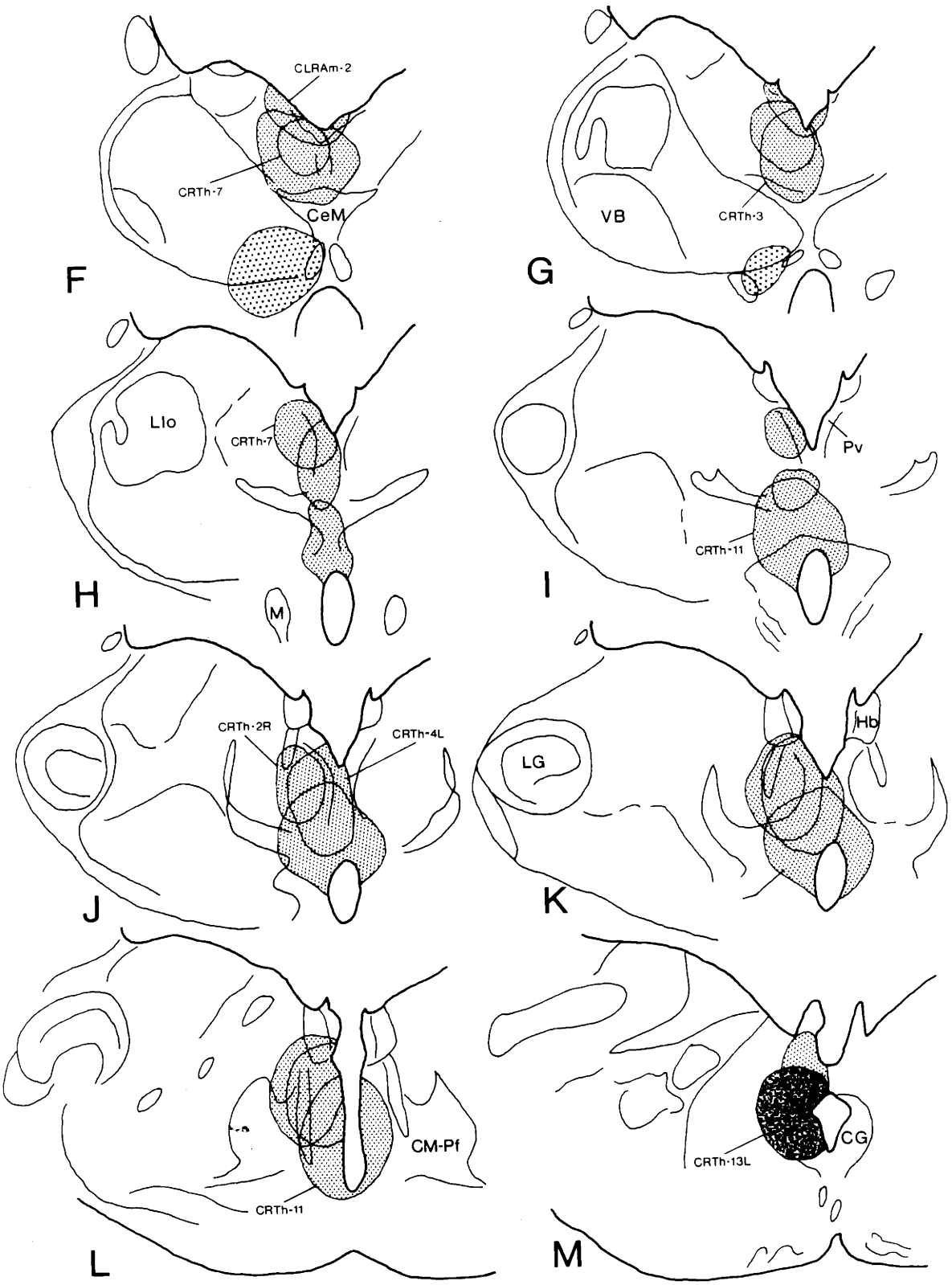
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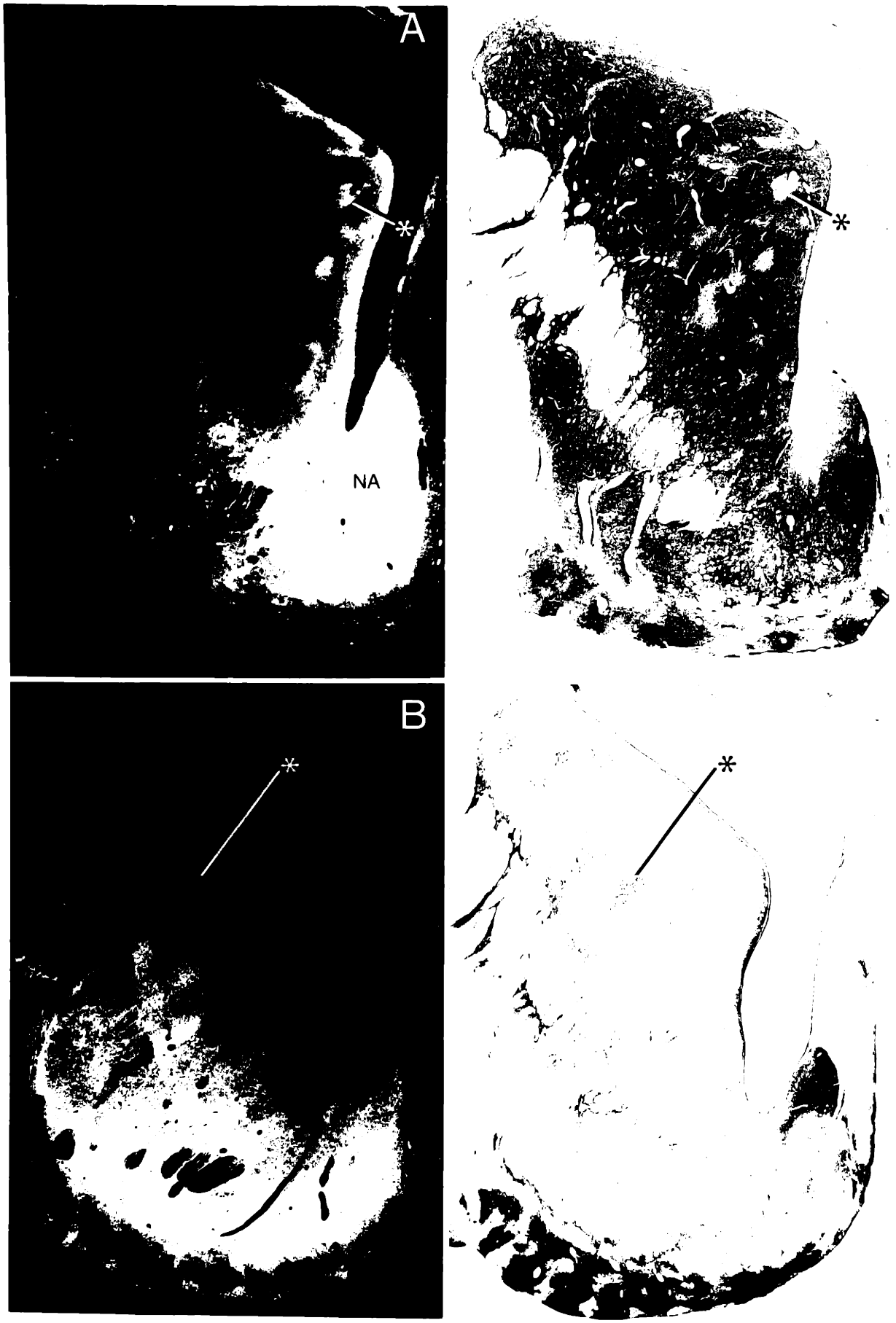
CRTh-4L
J
LG
Hb
K
CM-Pf
CRTh-11
L
CG
CRTh-13L
M

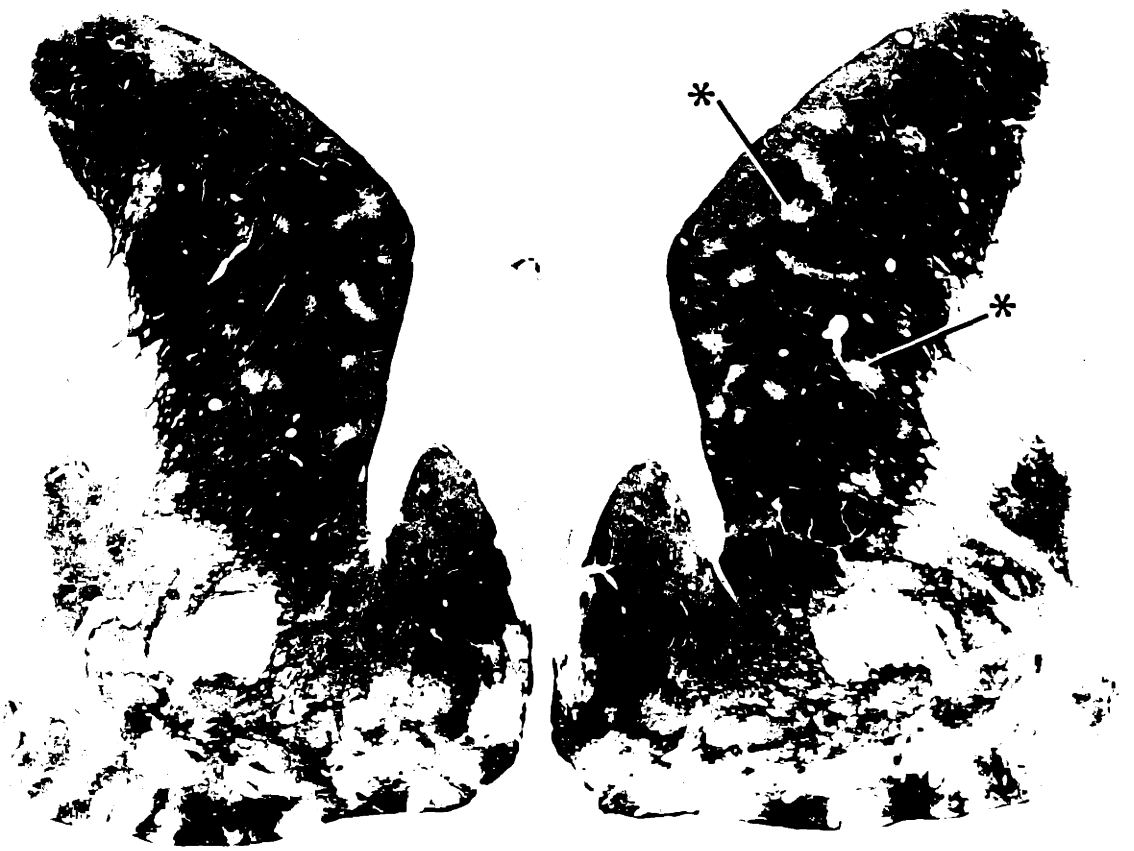
Figure 5-2: Relation between fiber-labelling (left) and histochemical staining for striosomes (right) seen after tracer-deposits involving the paraventricular nucleus of the thalamus at anterior (A: case CHRT-4R) and posterior (B: case CRTh-4L) longitudes. Asterisks mark correspondences between patches of fiber-labelling and zones of reduced AChE activity (A) or increased SP-like immunoreactivity (B) demonstrated in serially adjoining sections.


A
NA
B

Deposits involving the midline at mid-thalamic levels. Nearly all of the deposits that produced labelling of striosomes labelled striosomes on both sides of the brain. This was expected not only because these injection sites crossed the actual median plane; at least parts of the midline complex in the cat are genuine midline structures in that they are unpaired nuclei that project to both sides of the brain (Jayaraman, 1985; Groenewegen et al., 1980; Preuss and Goldman-Rakic, 1987). For our purposes this arrangement of bilateral connections proved vital in analyzing deposits placed at levels where the striatally projecting cells of the midline nuclei are confluent with those of laterally adjoining intralaminar complex. This was because the injections sites, though large, were without fail lopsided. It was therefore possible to carry out a subtractive analysis whereby what was common to the striatal labelling bilaterally was attributed to the part of the deposit that was symmetrical about the midline and what was added to the striatal labelling on the side favored by the deposit was attributed to the asymmetrical, and therefore off-midline, component of the injection site. This is dramatically illustrated in figure 5-3 for case CRTh-3. On the right side there are patches of labelled fibers in the caudate nucleus that coincide with the AChE-poor striosomes. On the left side the medial and ventral caudate nucleus is completely blanketed with labelled fibers; only in the lateral caudate nucleus can one on occasion see any differential labelling of the striosomes. Consultation of illustrations of the injection site for case CRTh-3 (Fig. 5-1:D-H) established that it was the left side of the brain that was favored by the deposit. We interpret this pattern as indicating that the midline core of the deposit led to selective labelling of striosomes whereas the off-midline intralaminar zone invaded on the left, at the least strongly innervates matrix tissue.

The labelling in this case was situated more centrally in the caudate nucleus

Figure 5-3: Compartmental pattern of fiber-labelling seen in case CRTh-3 following a large, lopsided deposit of radiolabelled amino acids at the thalamic midline. Serially adjoining sections prepared for autoradiography (top) and AChE histochemistry (bottom) demonstrate that fibers selectively innervate AChE-poor striosomes in the right caudate nucleus (marked by asterisks), but reach both compartments nearly equally in the left caudate nucleus.



than that seen after more rostral deposits. Labelling along the ventricular edge of the caudate nucleus was evident only dorsally; the medial strip at and ventral to the genu of the caudate nucleus was not labelled. As before, there was strong labelling of the ventral striatum.

Moderate matrix labelling was also evident in the right caudate nucleus (Fig. 5-3). Although this may have been due to partial encroachment by the deposit on the lateral thalamostriatal system, it does appear that the midline system provides some input to the ventral matrix. Case CRTh-7, in which the injection site was centered in the paraventricular nucleus at mid-thalamic levels (Fig. 5-1:F-I), offers the best evidence for ventral matrix innervation because, unlike more ventral or posterior injections, it did not involve the intralaminar nuclei and, unlike more anterior deposits, evidence of matrix labelling was not muddled by the presence of medial strip labelling. On the side of the brain favored by the deposit, there was strong, almost homogeneous labelling of the ventromedial caudate nucleus and clear labelling of striosomes through the central caudate nucleus. This matrix labelling could conceivably have been due to involvement of striatally projecting cells lateral to the paraventricular nucleus, but this possibility would not account for the striatal projection on the other side of this brain. There, although the overall labelling was weaker and the selective labelling of striosomes more pronounced, the ventral matrix was definitely innervated by labelled fibers.

Deposits in posterior medial thalamus. Unequivocal labelling of lateral striosomes was present in four cases. Figure 5-2B documents the compartmental labelling seen in case CRTh-4L, in which a large deposit of ^{3}H-amino acids placed in posterior medial thalamus infiltrated the caudal paraventricular and rhomboid nuclei and extended into the mediodorsal nucleus (Fig. 5-1:I-M). Marked patches of fiber-labelling were present in the lateral part of the caudate nucleus and these

labelled zones corresponded to striosomes demonstrated by SP immunohistochemistry (Fig. 5-2B). Interestingly, the labelling of dorsolateral striosomes appeared more clearly constructed of labelled *fibers* than did that of striosomes elsewhere. The medial strip was not labelled, but there was moderate labelling of matrix tissue in ventral parts of the caudate nucleus and putamen. The ventral striatum was heavily labelled. This labelling was stronger laterally than in the cases of more rostral injections, and the septal division of the nucleus accumbens, particularly caudally, was not strongly labelled.

The injection site in case CRTh-11 (Fig. 5-1:H-L), which principally involved the rhomboid and central medial nuclei, and the deposit in case CRTh-2R (Fig. 5-1:J-L), which mainly involved the caudal paraventricular nucleus, both elicited strong labelling of lateral striosomes similar to that seen in case CRTh-4L. Also evident in CRTh-11 on the side of the brain where the deposit expanded laterally and at rostral striatal levels in CRTh-2R, was moderate labelling in the medial part of the caudate nucleus. This labelling appeared to surround striosomes rather than to fill them. We attribute this 'avoid' pattern (see below) to the considerable involvement of the medial part of the parafascicular nucleus that was common to these injection sites and distinguished them from the deposit in case CRTh-4L.

In case CRTh-1, there was quite strong matrix labelling on the side of the brain favored by the deposit and, in addition, fairly weak labelling of lateral striosomes and of nucleus accumbens tissue bilaterally. The weakness of the striosome labelling in this case was presumably because the midline was only partially infiltrated by the deposit (Fig. 5-4:C1-G1). Finally, CRTh-2R was unique among the medial thalamostriatal cases so far described in not labelling striosomes on both sides of the brain, presumably because its labelling of the caudal paraventricular nucleus principally occurs behind the massa intermedia.

The labelling of striosomes after medial thalamic deposits was not restricted to the head of the caudate nucleus. In all of the cases, inhomogeneous labelling could be followed caudally at least into the body of the nucleus and, when reliable histochemical preparations were available, was found to occupy striosomes. The topography of the projection was also maintained, with anterior deposits labelling the medial margin of the caudate nucleus and medial striosomes and posterior deposits labelling striosomes in lateral caudate nucleus and putamen. Although striosomes are notoriously difficult to demonstrate in the putamen, we were able to confirm several instances of striosomal labelling there at intermediate and caudal levels (cases CRTh-11 and CRTh-4R; not illustrated). The putamenal labelling, when seen, was also notable for favoring the lateral and, especially, the medial margins of the nucleus.

Additional cases. Case CRTh-13L served as a control for the medial thalamic injections as its deposit was situated medially, in line with the deposits so far described, but caudal to the dorsal thalamus (Fig. 5-1:G). It covered the central gray substance but did not appear to encroach on either the paraventricular or the medial parafascicular nuclei. No labelled fibers were seen in dorsal or ventral striatum (or in the amygdala).

In case CLRT-1R a huge deposit of tracer was placed in ventromedial thalamus (Fig. 5-1:B-G). It involved the ventromedial nucleus and the nucleus reuniens and large parts of the dorsal hypothalamus, including the parvocellular nucleus of Rioch and the bed nucleus of the inferior thalamic peduncle (Bleier, 1961). This deposit evoked light to moderate labelling throughout the ventral striatum and in the ventrolateral caudate nucleus and putamen. In addition it elicited marked labelling of fibers in centrolateral caudate nucleus that collected both at the margins of and within AChE-poor striosomes. Although a somewhat

fibrous appearance to the innervation of striosomes was seen in the labelling of dorsolateral caudate nucleus, fiber-labelling along the boundaries of striosomes was not noted in any of the cases reviewed so far. We could not account for this dissimilarity in the character of the striosomal labelling by any incidental feature of this case, such as the length of the post-operative survival time.

Comment. Thalamic deposits that involved the rhomboid nucleus or all but the rostral pole of the paraventricular nucleus produced strong labelling of the ventral striatum and of striosomes in dorsal striatum. Label was also seen in ventral matrix tissue of the caudate nucleus and, following rostral thalamic injections, in a marginal strip along the ventricular face of the nucleus. The medial thalamic projection to striosomes appeared to be a single projection-system that was spatially organized in one dimension: rostral deposits labelled the striatum medially and caudal deposits labelled it laterally. A similar though more modest topographic shift was also seen in the projection to the ventral caudate nucleus and ventral striatum.

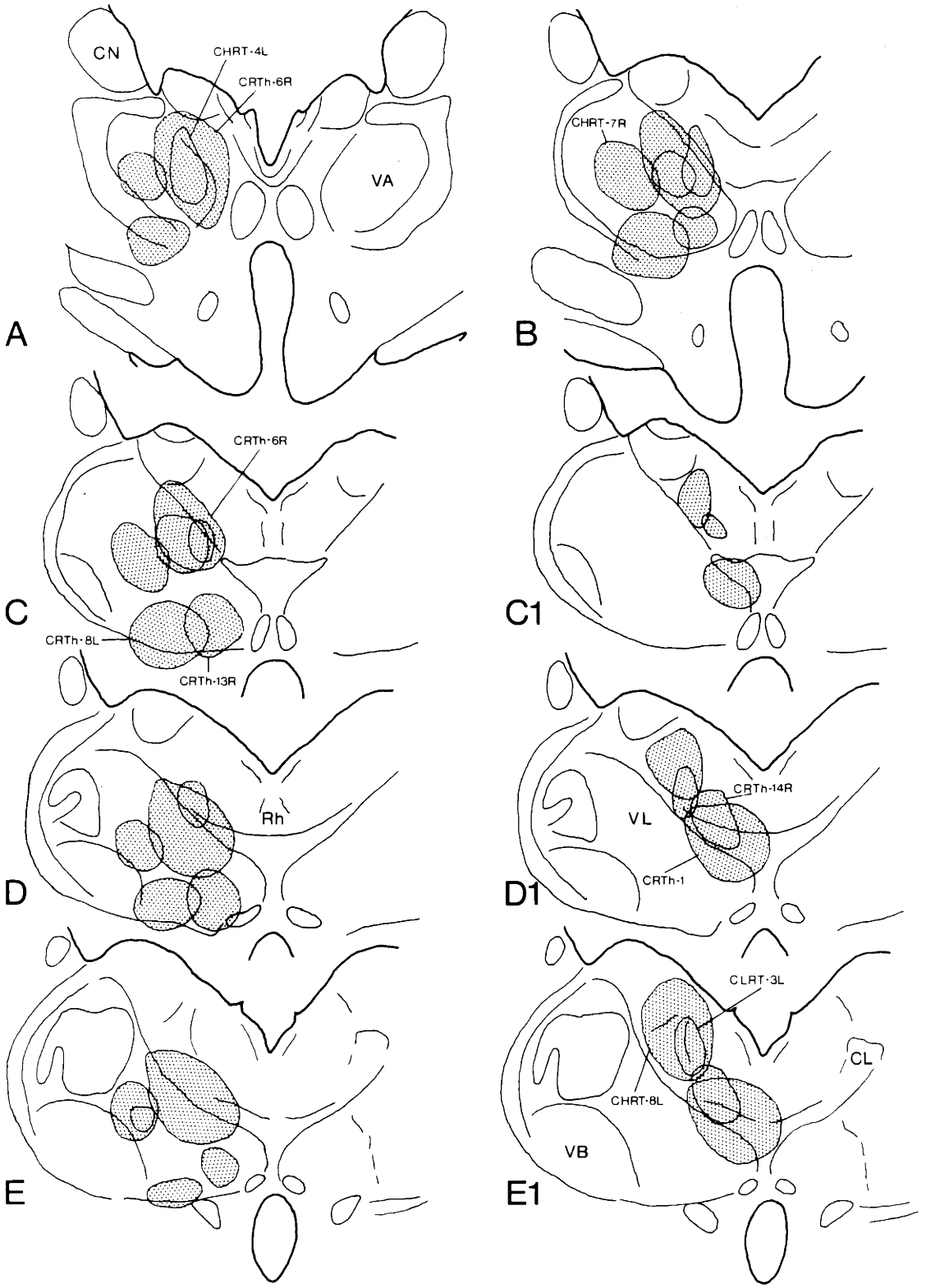
We do not know the source of the labelling of striosomes in case CLRT-1R. This deposit did not reach either the rhomboid or the paraventricular nuclei. It did quite heavily involve the ventromedial nucleus, including the region covered by case CRTh-13R. Some features of the fiber-labelling seen after ventral tier injections are similar to those seen in case CLRT-1R (see below); these nuclei, however, mainly innervate matrix tissue and, in fact, may account for the light labelling seen in the ventrolateral caudate and putamen in this case. No other sources for this projection are suggested by published maps of cells that project to striatum; it may have been missed, though, given that the deposit in case CLRT-1R is massive, the demonstrated projection is not heavy and the centrolateral caudate nucleus does not appear to have been injected with retrograde tracers in the studies we reviewed.

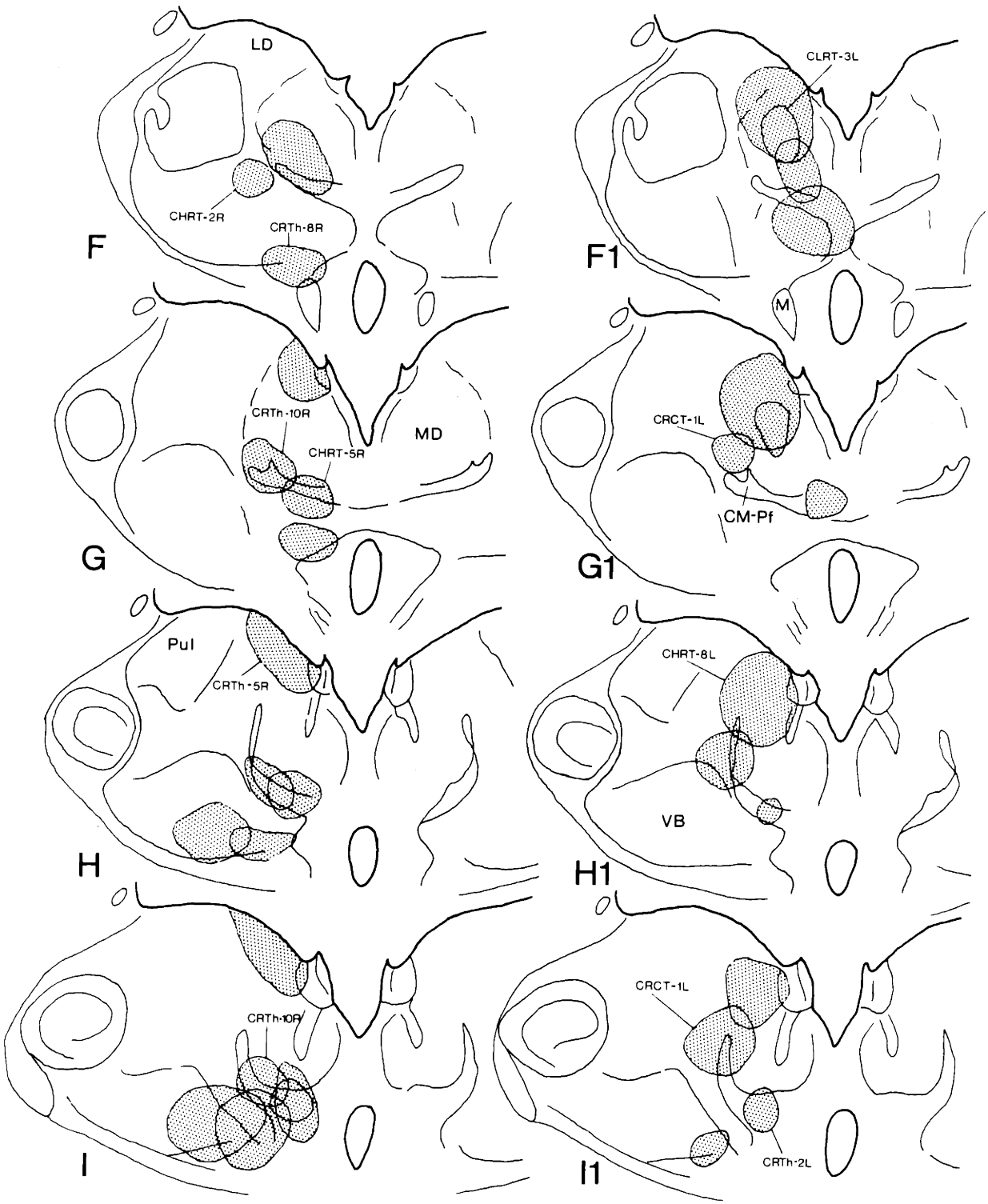
Cases that predominantly produced labelling of matrix tissue

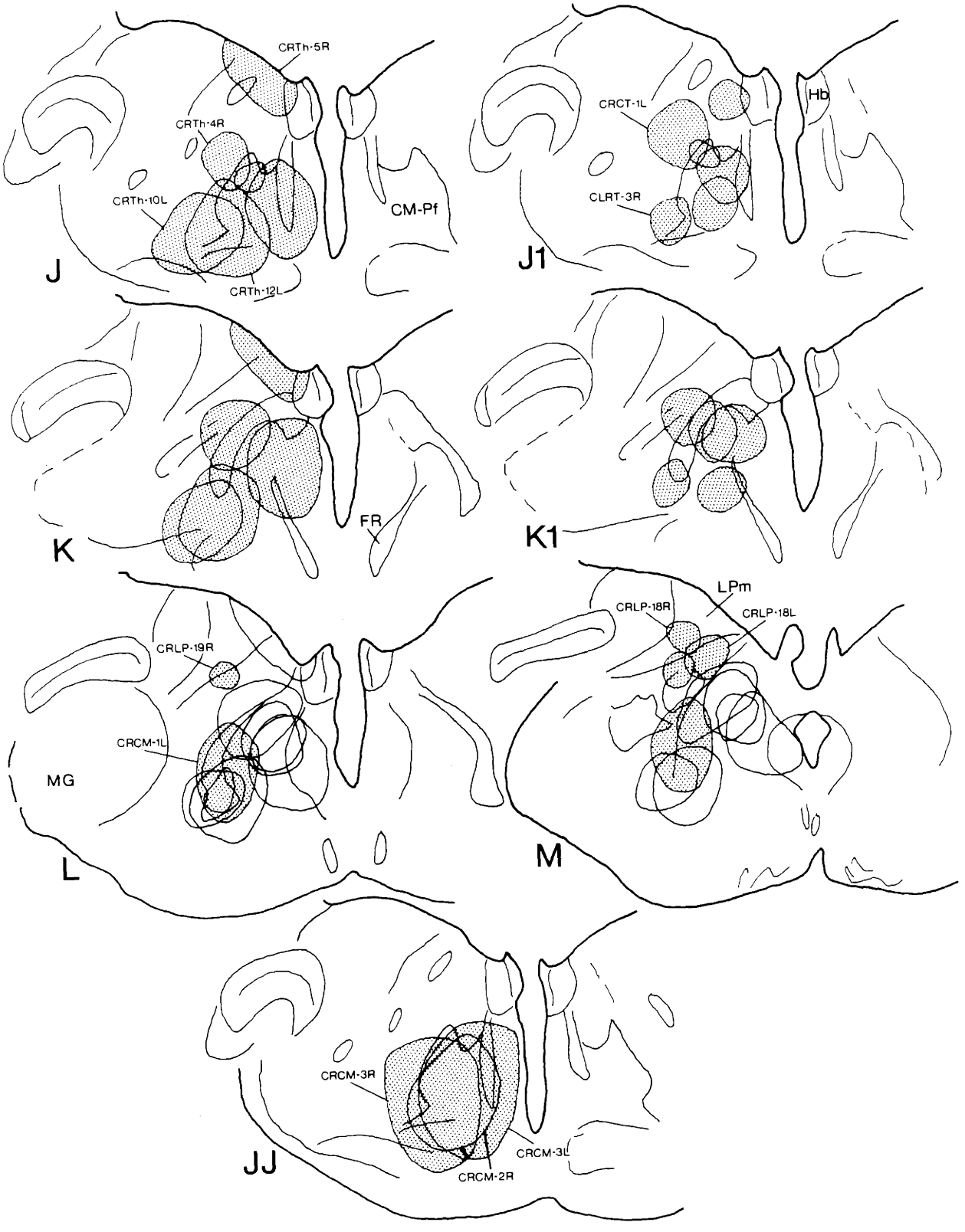
Deposits in ventral tier nuclei. Striatal projections arising principally from the ventral nuclear complex (ventroanterior, ventrolateral and ventromedial nuclei) were labelled in eight cases. The location and volume of the innervation varied across the experiments, but the pattern of termination, including the relationship with striosomes, remained similar. The medial caudate nucleus from its dorsal cap to its center, but not including the medial strip, was labelled in cases CRTh-6R (Fig. 5-4:A-D) and CHRT-4L (Fig. 5-4:A-C). The deposits in these cases principally involved the paralaminar ventroanterior nucleus and the anteromedial nucleus (see Fig. 5-5A). The dorsal putamen and lateral caudate nucleus, including the dorsolateral district that receives input from pericruciate cortex (see Chapter 4), was labelled in case CRTh-8L, in which the rostrolateral ventromedial nucleus and the ventromedial ventrolateral nucleus was injected (Fig. 5-4:A-E). The extreme dorsolateral corner of the caudate nucleus, which was not as densely labelled in this case as were other parts of the dorsolateral caudate nucleus, was selectively, though lightly, labelled after the deposit in the ventrolateral nucleus in case CHRT-7R (Fig. 5-4:A-E). Finally, deposits in the ventromedial nucleus were made in two cases. In case CRTh-13R (Fig. 5-4:B-E), fiber-labelling appeared in the central and ventrolateral caudate nucleus and in the ventromedial putamen. The injection site in case CRTh-8R was centered in the basal ventromedial nucleus, but included also the caudal end of the (principal) ventromedial nucleus (Fig. 5-4:F-G). In this case restricted fiber-labelling was seen in central and ventral putamen and in the lateral part of the ventral striatum, including the olfactory tubercle. In none of these cases could fibers be traced to the body or tail of the caudate nucleus, or to the caudal putamen.

Comparison of the distribution of the labelled fibers with patterns of AChE

Figure 5-4: Chartings of the lateral thalamic injection sites. Sections are arranged according to the scheme outlined in Figure 5-1. The caudal continuations of the K and K1 series are combined in L and M; for clarity, these continuations are *not* shaded in stipple. Three cases of large deposits of label into the posterior intralaminar group are illustrated by a single transverse level (JJ) corresponding to the longitude of J and J1.


A
CN
CHRT-4L
CRTh-6R
VA
B
CHRT-7R
C
CRTh-6R
CRTh-8L
CRTh-13R
C1
D
Rh
D1
CRTh-14R
VL
CRTh-1
E
E1
CLRT-3L
CL
CHRT-8L
VB


LD
CHRT-2R
CRTh-8R
F
CRTh-10R
MD
CHRT-5R
G
Pul
CRTh-5R
H
CRTh-10R
I
CLRT-3L
F1
M
CRCT-1L
CM-Pf
G1
CHRT-8L
VB
H1
CRCT-1L
CRTh-2L
I1


CRTh-5R
CRTh-4R
CRTh-10L
CM-Pf
CRTh-12L
J
CRCT-1L
Hb
CLRT-3R
J1
FR
K
K1
CRLP-19R
CRCM-1L
MG
L
LPm
CRLP-18R
CRLP-18L
M
CRCM-3R
CRCM-3L
CRCM-2R
JJ

staining, which was possible in every ventral complex case except CRTh-8R, established that the ventral tier connection was primarily with the matrix compartment (Fig. 5-5A). Reduced labelling in striosomes did not, however, account for most of the fiber-patterning seen in these cases. Microscopically, the labelling had a fibrous appearance and in areas of dense innervation, this gave a matted look to the grain-pattern (Fig. 5-5A). Macroscopically, there were broad inhomogeneities in the innervation of the matrix that were not due to striosome avoidance. Heterogeneity in the matrix was seen both in cases with light labelling, such as the ventrolateral and ventromedial nuclear injections, and in cases with dense labelling, such as CRTh-6R, when the exposure times for the autoradiography were short (for CRTh-6R, four weeks instead of the thirty-nine weeks illustrated). Some, but not all, of the matrix patterning appeared due to a preference by ventral complex projections for the vicinity of striosomes: labelled fibers were often seen to accumulate alongside the striosomes and, sometimes, to invade them partially. Because of these tendencies, the borders of the striosomes were not, as a rule, sharply defined in the autoradiograms.

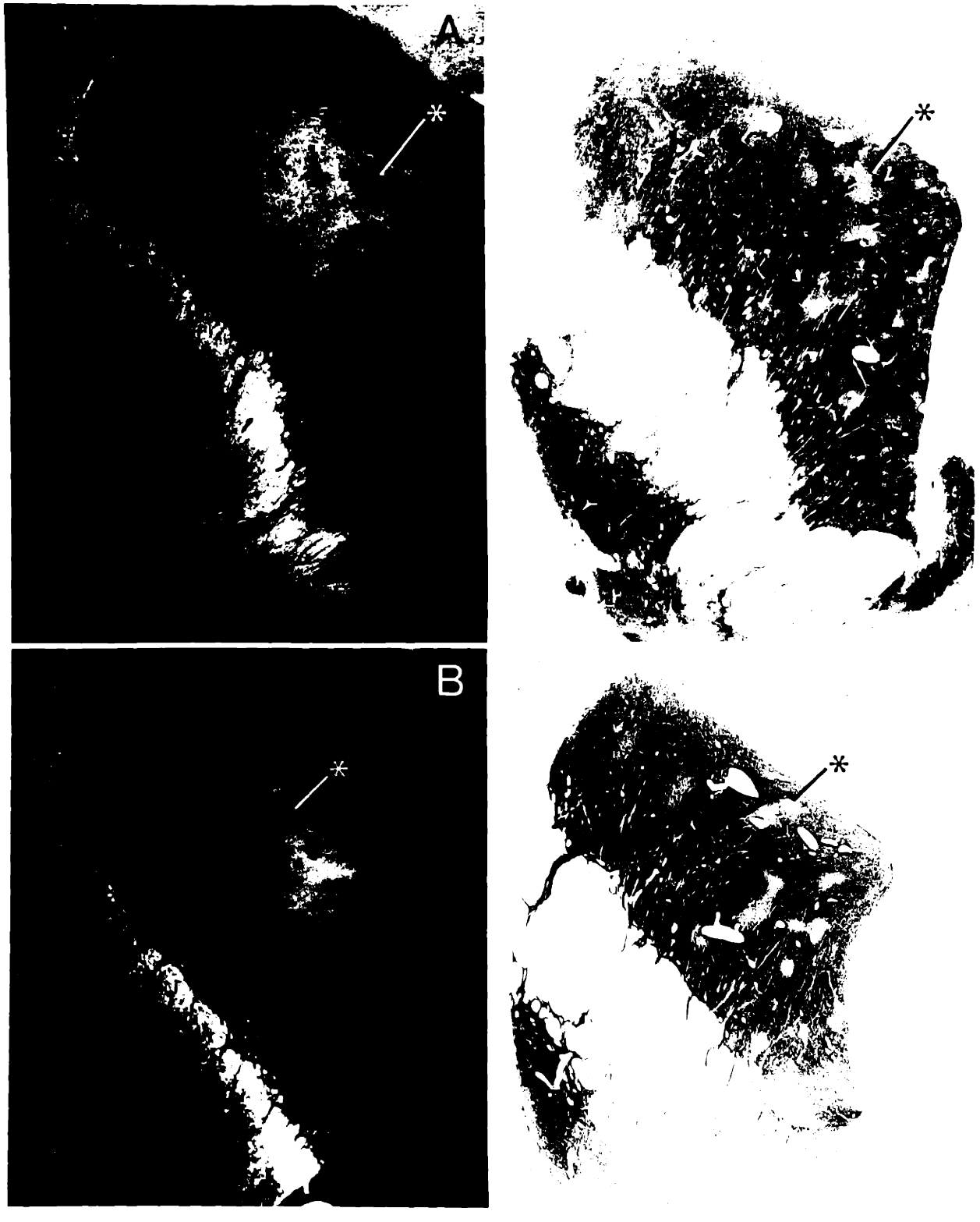
Comment. These observations confirm a widespread projection from the ventral thalamic complex to the striatum, as shown previously in the cat by retrograde transport methods (Royce, 1978a, 1983; Macchi et al., 1984; Beckstead, 1984a; Jayaraman, 1985; Takada et al., 1985b) (Royce, 1978a; Royce, 1983; Macchi et al., 1984; Beckstead, 1984a; Jayaraman, 1985; Takada et al., 1985b) and with anterograde autoradiography for the ventromedial nucleus of the rat (Herkenham, 1979) and the ventroanterior nucleus of the dog (Tanaka et al., 1986). Our anterograde observations in the cat establish that the projection is predominantly to the matrix compartment of the dorsal striatum. The connection has a straightforward spatial organization whose coordinate mapping can be visualized by a

transverse section through the ventral complex partially rotated in the clockwise direction and superimposed on a transverse section through the striatum. Tanaka et al. (1986) arrived at similar conclusions about the topography of the projection to the dorsal half of the caudate nucleus in the dog (see also Jayaraman, 1985).

It was not clear why the labelling elicited laterally in the caudate nucleus tended to be less dense than that seen dorsomedially or why a large ventral complex deposit such as that in case CHRT-7R should produce such modest and restricted striatal labelling. Possible explanations include that the projection to the lateral striatum is a more dispersed one or, more likely, that our lateral deposits were not centered on the source of the input to lateral striatum and strongly involved a part of the ventral complex that does not project to the striatum. Although some neurons in the ventrolateral nucleus are labelled after striatal deposits of retrograde tracers (Royce, 1983; Jayaraman, 1985), it has not been shown that all parts of the nucleus, including the motor cortex-connecting zone that lies beyond the distribution of pallidal and nigral fibers (Anderson and DeVito, 1982; Hendry et al., 1979), project to the striatum.

Deposits in anterior intralaminar nuclei. A very different pattern of matrix labelling was seen in the four cases where involvement of the thalamostriatal connection was substantially limited to the central lateral and paracentral nuclei and the para-stria medullaris district. To emphasize this difference, we have selected a case that elicited labelling of the same part of striatum as was labelled in case CRTh-6R (Fig. 5-5A)- that is, the dorsomedial and central caudate nucleus. Unlike the ventral complex injections, the anterior intralaminar deposits produced very few clearly-labelled fibers (Fig. 5-5B). Instead, the labelling-pattern was a fairly smooth and sometimes heavy diffusion of grains. Within the field of label, there were zones of clearly, but not dramatically, reduced grain-density. These

Figure 5-5: Fibers labelled by deposits of radiolabelled tracers placed in the ventroanterior nucleus (A: case CRTh-6R) and anterior intralaminar complex (B: case CLRT-3L) innervate extrastriosomal matrix. Asterisks mark correspondences between fiber-poor zones in the autoradiography (left) and enzyme-poor zones in the AChE histochemistry (right).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grain-poor zones correspond to striosomes (Fig. 5-5B). The borders of these zones were not sharply etched in the autoradiograms and where the grain-density was either low or quite high, it was often difficult to detect decrements of labelling over the striosomes. There was no evidence for inhomogeneities in the labelling of the extrastriosomal matrix.

In case CLRT-3L, which is illustrated in Figure 5-5, the deposit involved the anterior central lateral nucleus along with the lateral mediodorsal nucleus (Fig. 5-4:D1-G1). The striatal labelling in case CHRT-8L was quite similar to that seen in case CLRT-3L even though its injection site was much larger and included the para-stria medullaris district (Fig. 5-4:C1-J1). The other cases in this series showed a similar character to their pattern of striatal fiber-labelling and also avoided the striosomes, but differed in the striatal district they innervated. The deposit in case CRCT-1L, which was centered in the posterior central lateral nucleus and only slightly involved the dorsolateral part of the posterior intralaminar complex (Fig. 5-4:G-K), produced labelling of the dorsolateral caudate nucleus and dorsal putamen. The ventromedial caudate nucleus was labelled in case CRTh-14R. In this experiment, the deposit was centered in the middle of the mediodorsal nucleus, but did extend ventrally to involve the paracentral nucleus (Fig. 5-4:C1-F1). A projection from the paracentral nucleus to the ventromedial caudate nucleus was expected from the analysis of off-center midline injections presented earlier.

Case CRTh-5R. The deposit in case CRTh-5R overspread dorsomedial thalamus caudally, reaching from the lateral habenula across several divisions of posterior thalamus, and including the posterior half of the para-stria medullaris zone (Fig. 5-4:G-K). In the medial and ventral caudate nucleus, particularly caudally, there was a dense, diffusely granular labelling that clearly avoided striosomes. In the head of the nucleus, however, some of the labelling was fibrous

in appearance, there was a suggestion of matrix inhomogeneity and labelled fibers were clearly invaded some striosomes. There were also several candidate fibrous fills of striosomes (not illustrated).

Comment. The deposits in the anterior intralaminar nuclei (including the central lateral and paracentral nuclei and the para-stria medullaris zone) were not numerous enough to specify fully the spatial organization of this projection; the topographic shifts seen did appear to preserve, in rough fashion, the dorsoventral and mediolateral thalamic axes (see also Powell and Cowan, 1956; Herkenham, 1978), but we could not rule out a partial rotation in the mapping whereby caudal sites in the central lateral nucleus project somewhat more laterally in the striatum and rostral ones, more medially (Herkenham, 1978a). Interestingly, a clear mediolateral organization to the central lateral nucleus projection is indicated by the observation of mediolaterally-adjoining crescents of labelled neurons in the nucleus following deposits of distinguishable retrograde tracers in medial and lateral striatum (van der Kooy, 1979; C. Olson, personal communication). Because the central lateral nucleus is narrow, we should in fact have expected scant support for such a mediolateral topography to issue from thalamic deposits of anterograde tracers.

It seems likely that more than one thalamostriatal system was labelled in case CRTh-5R. The caudal para-stria medullaris zone appears a good candidate for the homogeneous matrix projection to caudal and medial caudate nucleus. The sources of both the fibrous matrix input and the suggested projection to striosomes are not clear.

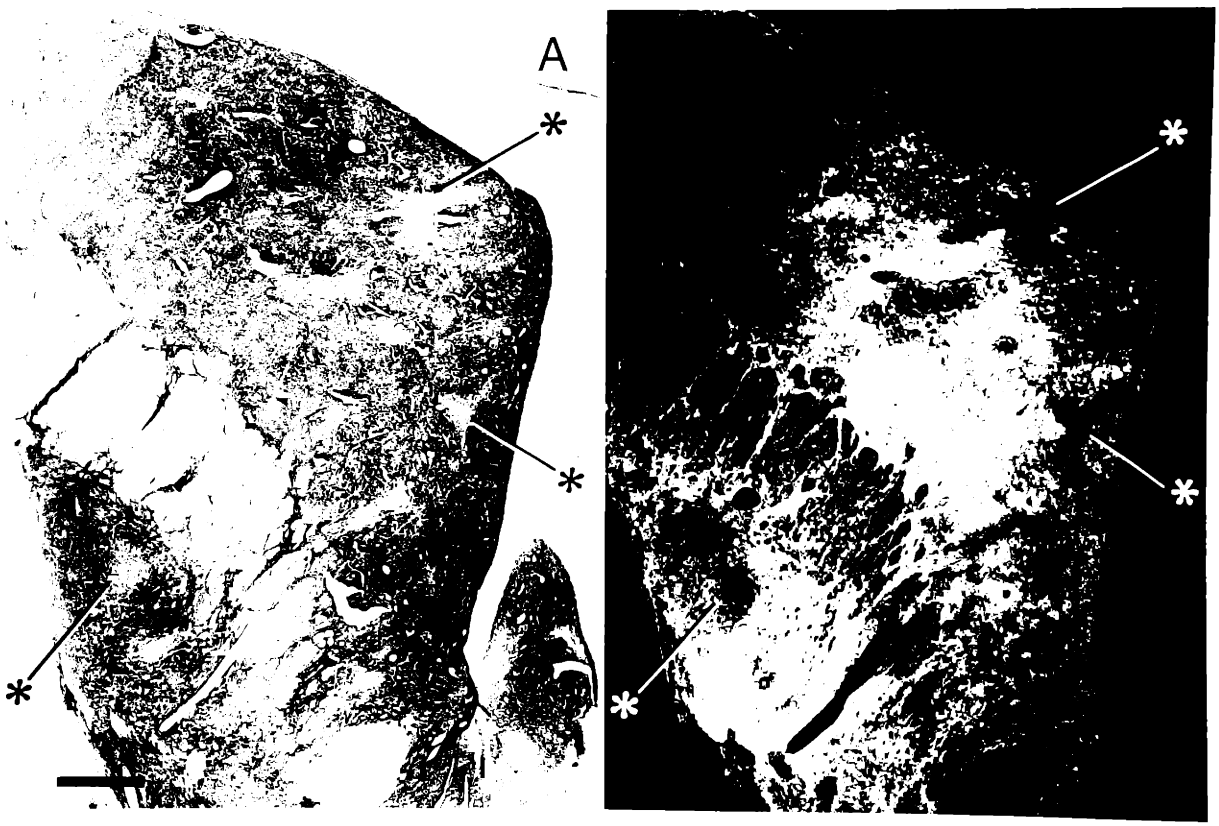
Deposits in the region of the centromedian and parafascicular (CM-Pf nuclei.) The striatal labelling elicited by deposits in the posterior intralaminar complex was studied in fifteen cases. We found, as did Beckstead (1984a) and

Royce and Mourey (1985), that the topography of the projection was one of roughly preserved spatial relationships in all dimensions. For example, deposits separated in the medial-lateral or dorsal-ventral axes, whether of moderate size and largely disjoint (CRTh-10R and CHRT-5R; Fig. 5-4G-I) or large and overlapping (CRCM-3R and CRCM-3L; Fig. 5-4JJ), produced striatal labelling that was correspondingly displaced in the appropriate dimension. The evidence for spatial organization in the anterior-posterior axis was not as commanding, but we did find that rostral injection sites, such as that in case CRTh-10R, did not label the caudal striatum whereas caudal deposits, such as that in case CLRT-3L, strongly favored this territory.

Two observations concerning the spatial organization of the projection were of particular note. First, deposits well removed from the midline and involving the ventrolateral CM-Pf complex and the adjoining subparafascicular nucleus-peripeduncular area cell-continuum (*e.g.*, case CRTh-10L), invariably produced strong and often selective labelling of the ventral division of the nucleus accumbens. Second, injections involving that motor cortex-recipient district of the posterior intralaminar complex (primate CM-like territory) produced labelling of the motor cortex-recipient district of the striatum (primate putamen-like territory; see Powell and Cowan, 1967). The deposit in case CRTh-10R (Fig. 5-4G-J) was particularly noteworthy in this regard as it elicited striatal labelling nearly coextensive with the district receiving input from pericruciate (sensory-motor) cortex.

The matrix compartment of the striatum was the primary target of fibers labelled after tracer-deposits in the posterior intralaminar complex (Fig. 5-6). Unlike the ventral complex or anterior intralaminar group cases, though, the character of the matrix labelling in this series varied markedly across the

Figure 5-6: Patterns of fiber-labelling observed in the striatum following tracer-deposits into the centromedian-parafascicular nuclear complex. A, fibers labelled by a large deposit situated near the center of the posterior intralaminar group (case CRCM-2R) innervate matrix tissue fairly evenly. B, fibers labelled by a deposit placed near the rostral pole of the complex (case CHRT-5R) show a markedly inhomogeneous pattern of matrix termination. Asterisks indicate locations of AChE-poor striosomes. Curved arrow in B (left) points to large patch of fiber-labelling that lies in matrix tissue (right). Its shape is not determined by the striosome-matrix boundaries. Scale bar in A marks 1mm.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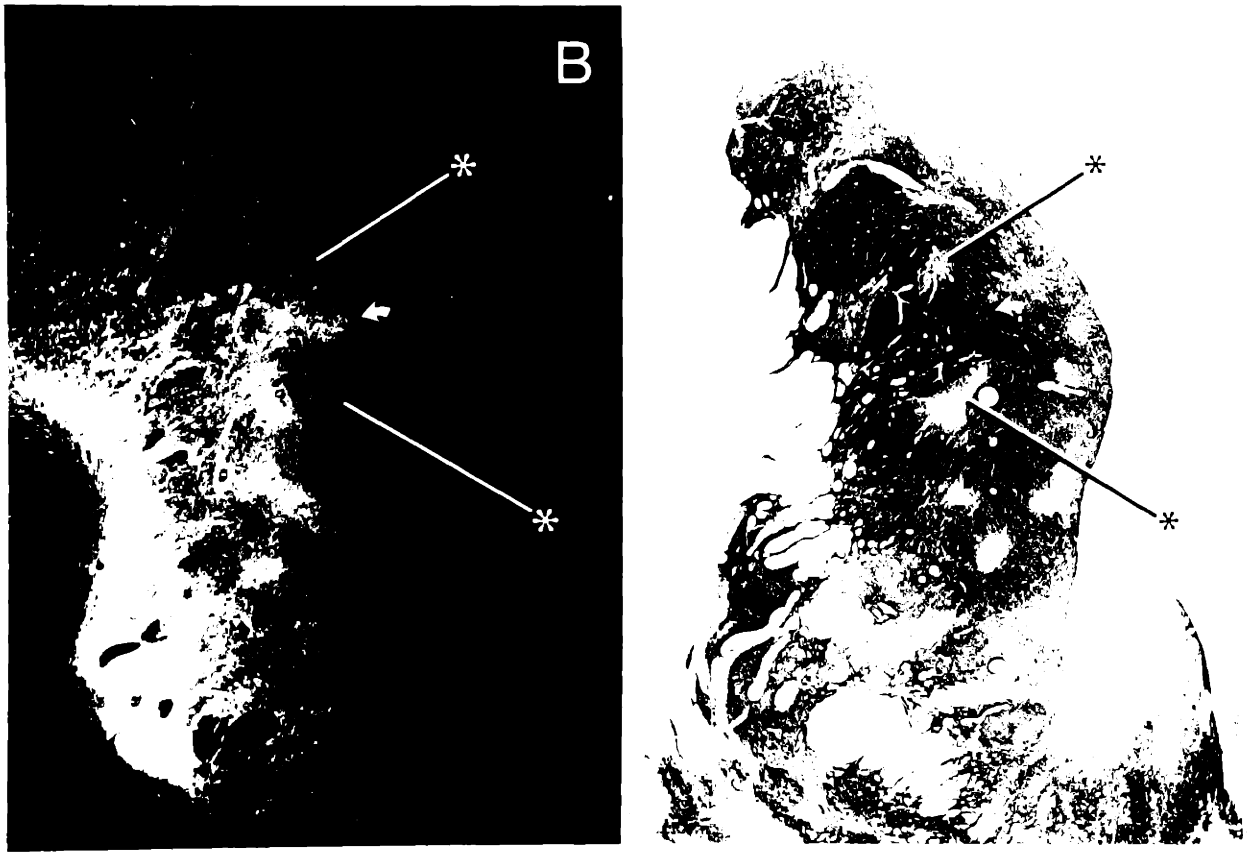

B

experiments. Massive tracer-deposits that covered most of the CM-Pf complex, such as that in case CRCM-2R (Fig. 5-4JJ), produced a fairly uniform field of matrix labelling, broken up by grain-poor zones spatially correspondent with the AChE-poor striosomes (Fig. 5-6A). More restricted deposits typically elicited a more heterogeneous pattern of matrix labelling. Figure 5-6B illustrates the arrangement of label seen in case CHRT-5R following a deposit of ^{35}S-methionine into a rostromedial part of the posterior intralaminar complex (Fig. 5-4G-I). The AChE-poor striosomes are clearly zones of reduced label; however, their disposition does not account for the large-scale grain-figures seen in the autoradiography. Other deposits elicited matrix inhomogeneities that tended to be smaller, and were often situated in the tissue immediately adjoining striosomes. The quality of the fiber-labelling also varied across the cases; in some experiments it was diffuse and in others it was strongly fibrous. Finally, in many cases we saw labelled fibers innervating striosomes in the lateral caudate nucleus. In all examples, though, the labelled fibers were predominantly located in the matrix compartment.

Comment. Matrix labelling-patterns similar to both the diffuse grain-distribution associated with the anterior intralaminar group deposits and the more complex, fibrous grain-patterning noted in the ventral complex cases were observed after CM-Pf deposits. In fact, the matrix inhomogeneities and striosomal fiber-labelling were more marked in this material than in other lateral thalamic cases. This variety in the character of the matrix labelling could not be accounted for by differences across experiments in the tracer used, survival time permitted or in the degree of involvement of striatally projecting cells located next to the CM-Pf complex in the caudal central lateral nucleus or the posterior thalamus. The posterior intralaminar deposits did, of course, differ in their locations so it seems reasonable that there might be components of the complex distinguished according

to the pattern of matrix labelling evoked. However, the well-documented topography to the striatal projection (Beckstead, 1984a; Royce and Mourey, 1985), which we have confirmed, would appear to account for the three-dimensional organization of the complex. We did note a tendency for rostral (and dorsal) connections to produce extrastriosomal patches and for lateral, CM-like projections to have greater access to the striosomal compartment.

Deposit in posterior thalamus that labelled the somatic sensory-recipient sector of the striatum. The injection site in case CHRT-2R, by the evidence of AChE histochemistry (Graybiel and Berson, 1980), was situated rostrally, where the lateral medial-suprageniculate nuclear complex (LM-Sg) merges with the ventral lateral intermediate nucleus, and partially implicated the ventrobasal complex (Fig. 5-4:E,F). By its position and cortical connections, this deposit included the anterior pole of the medial division of the posterior nucleus (Tanji et al., 1978; Burton and Kopf, 1984a). Fiber-labelling in the striatum was restricted to the dorsolateral caudate nucleus and dorsal putamen where it was distributed somewhat diffusely, with zones of reduced labelling and some patches of intense labelling. Projections from the region of the rostral posterior nuclear group to the dorsolateral caudate nucleus of the cat have been previously documented by both anterograde and retrograde techniques (Graybiel, 1972; Beckstead, 1984a,b). Comparison of the autoradiograms with serially adjoining sections stained to show SP-like immunoreactivity established that the labelled projection was restricted to the extrastriosomal matrix.

Deposits in posterior thalamus that labelled the caudal caudate nucleus and putamen. In six cases, deposits not implicating any intralaminar nuclei were successfully placed in posterior thalamus. After tracer-injections restricted to the medial division of the lateral posterior nucleus (LPm), labelled fibers were observed

caudally, in the lateral caudate nucleus and along the lateral margin of the putamen (case CRLP-18R; Fig. 5-4:M). More medial injections involving the LM-Sg complex also exhibited labelling along the lateral margin of the caudal putamen; in addition, there was some medial putamen labelling and the label in the caudate nucleus was shifted ventrally (cases CRLP-19R and CRLP-18L; Fig. 5-4:L,M). In case CRCM-1L, which involved the ventromedial part of the caudal LM-Sg complex along with the adjoining CM-Pf complex (Fig. 5-4:L-M), the labelling was also restricted to the caudal striatum; fibers in this case accumulated in the ventral caudate nucleus and medial putamen but were not seen along the lateral margin of the putamen.

Comment. Demonstrating striosomes in the caudal striatum is, at best, a capricious undertaking, so we did not determine the relationship between labelled posterior thalamic fibers and the distribution of the striosomes in these cases. Moreover, we were not successful in making more rostral deposits restricted to the LM-Sg complex (or the caudal division of the lateral intermediate nucleus) that might have produced more central striatal labelling (retrograde data of Beckstead, 1984a; Hu and Jayaraman, 1986). We suspect, though, that the posterior thalamic input is to the matrix compartment. First, the fiber-labelling in these cases, though somewhat patchy, had too broad a distribution to be restricted to the striosomal compartment. Second, larger injections of posterior thalamus, such as cases CRCM-1L and CRTh-4R (Fig. 5-4:J-K), which also involved the posterior intralaminar complex, elicited labelling that was mainly or exclusively in the extrastriosomal matrix.

Projections from lateral posterior thalamus to the striatum have been well-documented in the cat (Heath, 1970; Heath and Jones, 1971; Graybiel, 1972, 1973; Royce, 1978a; Beckstead, 1984a; Takada et al., 1985a,b; Hu and Jayaraman, 1986).

Graybiel (1973) suggested on the basis of degeneration techniques that posterior thalamic input to the putamen is arranged as a LP-recipient zone situated laterally and a posterior nuclear group-recipient zone situated centrally. This conclusion is supported by the HRP-WGA transport studies of Takada et al. (1985a). In anterograde autoradiographic experiments, Berson (1980) found that tracer-deposits in the pulvinar and lateral division of the LP that did not also involve the LPm failed to elicit striatal labelling. The observations reported here indicate that the visually-affiliated LPm projects to the lateral flank of the posterior putamen and the caudolateral caudate nucleus. Similar projections appear also issue from the adjoining (also visually affiliated- Olson and Graybiel, 1987) part of the LM-Sg complex, but not, apparently, from all parts of the complex. We observed labelling in more central and medial putamenal sites in every case in which the LM-Sg complex was involved, including those parts of the complex allied with auditory cortex (Bowman and Olson, 1986). In experiments on cortical input to the striatum (see Fig. 6-14 in Chapter 6), we have found that the caudolateral caudate nucleus and lateral margin of the caudal putamen (that is, the LPm-recipient districts) are the targets of projections from area 19 and that the ventrolateral caudate nucleus and caudocentral putamen are connected with auditory cortex. The caudomedial putamen may be in receipt of a more diverse input that includes sensory association cortex. This suggestion that thalamic input follows that from cortex in establishing adjoining visual and auditory zones in the posterior striatum has also been put forward by Lin et al. (1984) based on comparable data in the squirrel.

Fiber-labelling observed in the ventral striatum

The dense labelling seen in the nucleus accumbens after every medial thalamic deposit was heterogeneously distributed and often followed the

arrangement of histochemically identified tissue compartments (see Chapter 2 and 4). Rostrally, in the dorsal division of the nucleus accumbens, there are zones rich in BuChE activity and SP-like immunoreactivity. In most of the cases eliciting labelling of striosomes, these zones were selectively innervated by labelled fibers. In the remaining cases, the BuChE-positive zones were labelled as part of a strong though more homogeneous innervation of the dorsal division. By contrast, circumscribed zones of reduced staining for AChE activity and SP-like immunoreactivity appear in the septal division of the nucleus accumbens, and these were avoided by labelled thalamic fibers in every example we studied. The BuChE-poor border islands of the nucleus accumbens, which are distributed along the ventral and medial boundaries of the nucleus, were either free of labelled fibers or, if innervated, were zones of markedly reduced label compared with that seen in adjacent tissue of the nucleus accumbens.

Projections to the nucleus accumbens were also noted after lateral thalamic deposits. In no case were the septal zones or the border islands labelled. In the few cases (*e.g.*, CHRT-8L) where the grain-density in the anterodorsal nucleus accumbens was sufficient to permit comparison with the histochemistry, labelled fibers were seen to avoid the BuChE- and SP-rich zones.

Labelling in the olfactory tubercle, when present, was principally found in the two cellular layers and the deep, or dorsal, half of the molecular layer of the cortical zones (terminology of Meyer and Wahle, 1985). The flanks of the hila of the cap zones were sometimes labelled, but otherwise these zones, including the islands of Calleja and the hila themselves, were not innervated. The large, medial island of Calleja was never labelled.

Comment. The finding that the medial, but not the lateral, thalamic deposits labelled the BuChE-rich zones in the anterodorsal nucleus accumbens supports an

assignment of these zones to the striosomal system (see Chapter 4). Neither thalamic division, though, was observed to innervate selectively other histochemically and cytologically marked zones of the ventral striatum, such as the border islands, the septal zones and the islands of Calleja. Particularly in the ventral division of the nucleus accumbens, the input from the two projection-systems appeared to be, at the least, overlapping.

Somewhat similar data have been reported in the rat by Herkenham et al. (1984). They found that fibers travelling from the paraventricular, paratenial and central medial nuclei to the nucleus accumbens avoid the medial island of Calleja and cell-clusters rich in opiate binding sites. From their positions and appearance, a large proportion of these cell-clusters appear homologous to the border islands we have described in the cat (Ragsdale and Graybiel, 1987).

Fiber-labelling observed in the amygdala

A number of the thalamic deposits produced labelling of the amygdala. We found that we could assign nearly all of these cases to one of two groups according to whether the labelling present in the basolateral complex was in the basolateral nucleus or in the lateral and basomedial nuclei. Only three deposits resisted such classification: a posterior one involving tissue beside the habenular complex (case CRTh-5R described below) and two anterior ones, placed at the rostral pole of the thalamus, that strongly involved the paratenial nucleus. For the rostral deposits (CHRT-1 and CLRT-1L), the labelling elicited in rostral amygdala was dense in the dorsolateral part of the basomedial nucleus. Caudally the fibers shifted into the medial basolateral nucleus and, in much reduced number, to the rest of the dorsal basolateral nucleus.

The cases presenting strong labelling of the basolateral nucleus were precisely those that involved midline thalamus and produced labelling of the striosomes (that

is, the deposits displayed in moderate stipple in Fig. 5-1 and CRTh-1 in Fig. 5-4:C1-G1). We saw clear-cut differences in the disposition of the labelled fibers between the rostral and caudal deposits; the caudal deposits (CRTh-11, CRTh-4L, CRTh-2R) produced labelling that included the 'pedicle' of the basolateral nucleus while fibers labelled from more rostral injection sites were restricted to the dorsal half of the nucleus. There was also a slight tendency evident in a few of the cases for rostral injection sites, such as CLRAm-2, to favor the medial part of the nucleus and for caudal ones, such as CRTh-11, to favor the lateral part.

There was labelling elsewhere in the amygdala in these cases. The lateral central nucleus presented a pattern of marked and markedly heterogeneous fiber-labelling. This pattern consistently conformed to the arrangement of histochemical inhomogeneities noted in the nucleus and will not be described here. The intercalated cell masses and particularly the caudal ones, were standardly labelled. In some of the cases, most notably those with caudal injection sites such as case CRTh-4L, a sizable contingent of fibers accumulated in the medial and medial central nuclei and, from there, cut deep to the amygdalohippocampal area and wrapped around the bulk of the basomedial nucleus, thereby traversing the tissue that joins the periamygdaloid cortex and the basomedial nucleus. Finally, in case CRTh-11 on the side with the more extensive deposit, there was labelling of the rostromedial lateral nucleus. It seems likely that this was due to injection site involvement of lateral nucleus-projecting structures described below.

The balance of the cases presenting amygdaloid connections showed labelling in the lateral and basomedial nuclei. This labelling proved to be quite dense following deposits in the centromedian-parafascicular nuclear complex that extended ventrally (CRCM-2, CRCM-3) and ventrolaterally (CLRT-3R, CRTh-10L, CRTh-12L) to involve the subparafascicular nucleus and the cell-continuum

running from it to the peripeduncular area (Mehler et al., 1981). Injection sites in the posterior intralaminar group that did not involve this cell mass (e.g., CRTH-2L) did not exhibit connections with basolateral amygdala. The dominant impression taken from examination of the labelling-pattern in these cases was of a massive fiber-termination in the amygdala that carefully surrounds the basolateral nucleus. In all of these cases, fibers reached both the medial part of the lateral nucleus and the lateral part of the basomedial nucleus, thereby outlining the basolateral nucleus. The labelling covered nearly the full lateral nucleus and all but a ventromedial zone of the basomedial nucleus in a few cases. The lateral central nucleus was broadly labelled; the only part of the nucleus that labelled fibers consistently avoided was an acetylcholinesterase-poor region located dorsal to the basolateral nucleus (the γ region; see Ragsdale and Graybiel, 1987 for nomenclature). Strong fiber-labelling was also noted in the posterior substantia innominata, the medial central nucleus and all but layer 1 of the medial nucleus. The amygdalohippocampal area and the rostral periamygdaloid cortex were not labelled.

A much more restricted pattern of amygdalar labelling was observed after several deposits situated in off-midline dorsal thalamic sites. In case CLRT-1R there was, in rostral amygdala, strong labelling of the dorsomedial part of the lateral nucleus and the centrolateral part of the basomedial nucleus. The medial nucleus was moderately labelled and there were scattered fibers through the central nucleus and light labelling of layer 1 of the periamygdaloid cortex. In addition, the molecular layers of the medial nucleus and the posterior cortical nucleus were intensely labelled. The injection site in CLRT-1R was massive and heavily involved the rostral ventromedial thalamus and dorsal hypothalamus, but from retrograde tracing studies it seems likely that the source of the projection to basolateral

amygdala was the ventral nucleus reuniens (Russchen, 1982b). In two cases we saw labelling of a band of fibers stretching from the putamen through the lateral part of the lateral central nucleus to accumulate as a slab rostromedially in lateral nucleus: CRTh-8R, for which the labelling was quite heavy, and CRTh-13R. The tracer-deposit in case CRTh-13R, though much smaller than that of CLRT-1R and largely confined to the ventromedial nucleus, appeared to have somewhat invaded the ventral nucleus reuniens; cases such as CRTh-8L that were situated in more lateral parts of the ventromedial nucleus showed no amygdalar labelling. The injection site in CRTh-8R was caudal to that of CRTh-13R and, though it was centered in the basal ventromedial nucleus, did include part of the interventral nucleus (cf. Russchen, 1982b). Involvement of the interventral nucleus may also explain the very light labelling of the medial lateral nucleus that we saw in case CHRT-5R.

Finally, case CRTh-5R, like the cases involving the rostral pole of the thalamus, elicited a fairly complex arrangement of amygdalar labelling that could not be easily classed with either the basolateral or the lateral-basomedial patterns. There was in rostral amygdala marked labelling of the lateral margin of the lateral nucleus and a modest gathering of fibers over the basolateral nucleus. At more caudal levels the fibers over the basolateral rapidly parted to label the lateral basomedial and the medial basolateral nuclei. There was also isolated fiber-labelling in the lateral central nucleus. The injection site in this case covered several divisions of posterior thalamus and included tissue adjoining the stria medullaris caudally and the lateral habenula. This latter tissue appears by the evidence of retrograde tracing experiments to project to the amygdala (Russchen, 1982b); its full nuclear allegiances, however, remain uncertain and, given the pattern of labelling we saw in the amygdala, are possibly multiple. The LM-Sg

complex could be one contributor. Injections that involved the caudal LM-Sg complex but not the juxta-habenular zone (CRLP-18L, CRLP-19R) did elicit labelling in rostrolateral part of the lateral n. which extended into the medial part of its dorsal panhandle. Control injections into LPm did not label the amygdala (CRLP-18R), which appeared to exclude a contributory projection from this division. Except for animal CRCM-1, for which the relevant tissue was unavailable, none of our remaining thalamic cases showed fiber-labelling in the amygdala, including cases CHRT-8L, CRCT-1L and CRTh-4R, whose injection sites extended into caudal para-stria medullaris territory and the LM-Sg complex. This absence of labelling was probably because these amygdala-projecting zones were not at the centers of the deposits.

Comment. Anterograde evidence for thalamo-amygdalar connections in the cat is fairly scarce. Data from degeneration studies indicates a projection to basolateral amygdala from posterior thalamus (Graybiel, 1972a; Graybiel, 1973; Heath and Jones, 1971a) and there is evidence from anterograde transport of HRP-WGA for a projection from the vicinity of the basal ventromedial nucleus to the lateral nucleus (Yasui et al., 1987). Our autoradiographic cases confirm both of these projections and specifically attest to a projection from at least the lateromedial-suprageniculate nuclear complex to the lateral nucleus. Autoradiographic evidence for a presumably homologous projection from the medial pulvinar has been described in the monkey (Jones and Burton, 1976).

The only general description of thalamo-amygdaloid projections based on anterograde tracing techniques is a study in the rat reported in abstract form (Turner and Herkenham, 1981). The connection has, though, been extensively studied with retrograde tracing methods in several species, including the cat (Russchen, 1982b; Mehler et al., 1981; Ottersen and Ben-Ari, 1979). Our

observations agree quite well with the anterograde data of Turner and Herkenham (1981) and with the most detailed of the retrograde studies, that of Russchen (1982b). The only consequential dissimilarity between our findings and those of Russchen is that she attributes retrograde labelling of the ventral nucleus reuniens seen after amygdalar injections to involvement of the basolateral nucleus. Our autoradiographic deposits that appear to involve this thalamic zone suggest, instead, a projection to the lateral or basomedial nuclei.

In summary, all our deposits involving the paraventricular, rhomboid and central medial nuclei of the thalamic midline and producing labelling of striosomes in dorsal striatum, elicited dense and selective labelling of the basolateral nucleus of the amygdala. All other thalamic injections producing amygdalar labelling involved para-midline and meso-diencephalic border sites and labelled the lateral and basomedial nuclei of the amygdala.

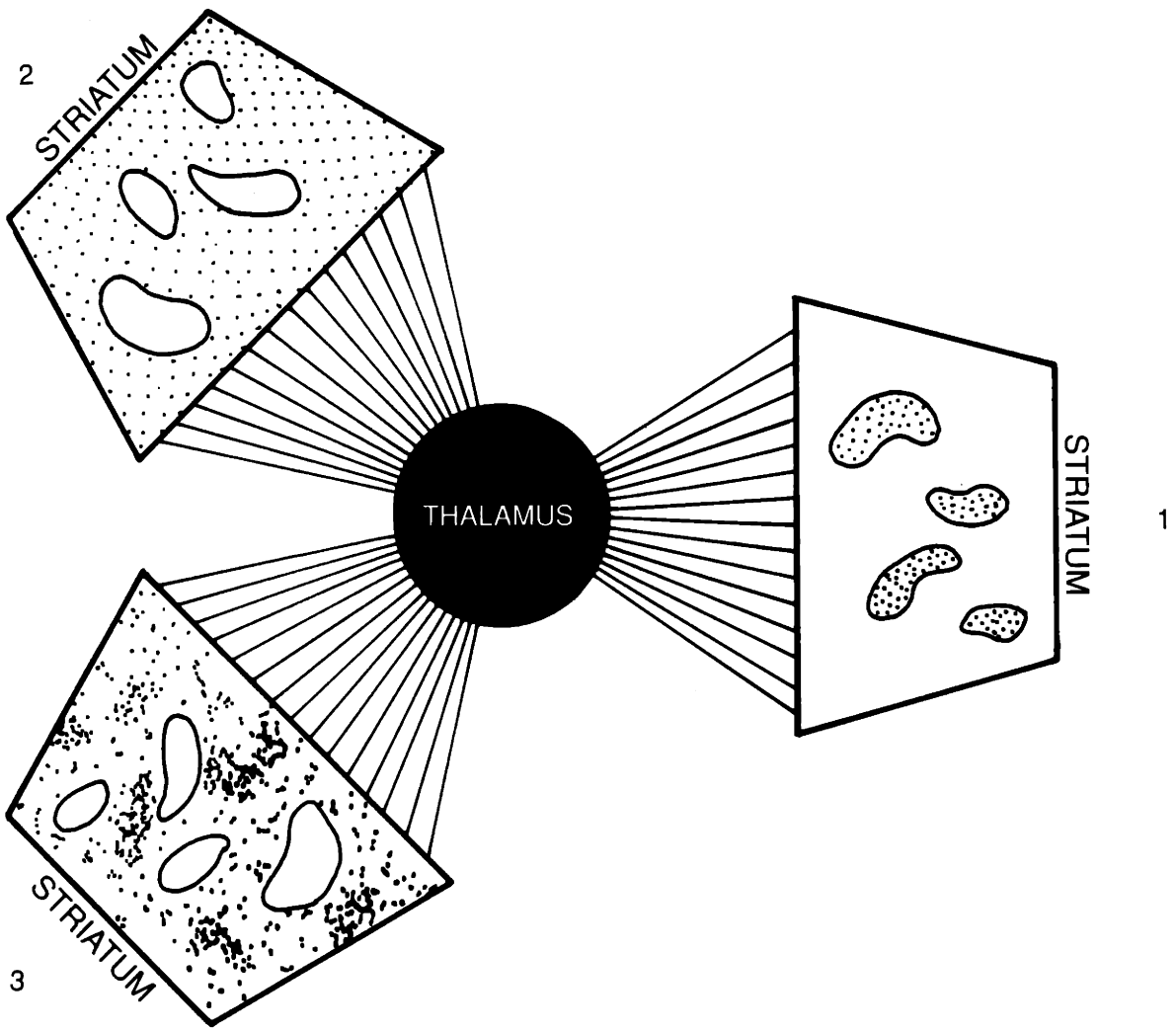
Discussion

We saw three basic patterns in the thalamic projection to dorsal striatum-innervation of striosomes, innervation of matrix evenly and diffusely, and innervation of matrix in a fibrous and inhomogeneous manner (see summary in Fig. 5-7). These patterns, considered in conjunction with the positioning of the thalamic deposits, the configuration of thalamostriatal nuclei and the topographic organization of the observed projections, suggested the presence of at least four thalamostriatal projection-systems: a medial one to striosomes and three lateral ones to matrix tissue.

The medial thalamostriatal system

Deposits of anterograde tracers involving those parts of midline thalamus that project to the dorsal striatum elicited labelling of striosomes. Every one of these thalamic cases also evoked labelling in ventral matrix tissue, the nucleus accumbens

Figure 5-7: Schematic representation of the compartmental organization of thalamostriatal projections in the cat as established by anterograde tracing studies. The illustration is adapted from Macchi's description (Macchi, 1983) of multiple thalamocortical systems distinguished according to the breadth of their innervation of cortex. Illustrated on the right is the medial thalamostriatal system (1), which originates in midline thalamus and distributes principally to striosomes. Two of the matrix-projecting, lateral thalamostriatal systems are described on the left: (2) the anterior intralaminar nuclei, which project diffusely and evenly to matrix; and (3) the posterior intralaminar nuclei, which project mainly to matrix tissue in a more heterogeneous manner.


2
STRIATUM
THALAMUS
STRIATUM
1
STRIATUM
3

and the basolateral nucleus of the amygdala. The rostral deposits in this group produced labelling of medial striosomes and of the strip of tissue that lies along the ventricular face of the caudate nucleus. Progressively more lateral striatal labelling occurred with successively more caudal placement of injection sites. Analysis of the configurations of our deposits, in consultation with the detailed maps of thalamostriatal neurons available in the cat (Beckstead, 1984a; Jayaraman, 1985), suggests that the sources of the projection to striosomes must include the paraventricular and rhomboid nuclei of midline thalamus. This is because both nuclei can be retrogradely labelled from injections placed in *dorsal* caudate nucleus. By contrast, the striatal connections of the central medial and paratenial nuclei are mainly with ventral striatum and ventral caudate nucleus (Groenewegen et al., 1980; Beckstead, 1984a; Jayaraman, 1985), so we can not conclude that these nuclei project to striosomes even though they were implicated in several of the medial thalamic cases.

Because of the large size of our deposits, we are unable to determine the lateral limits of the striosome-connecting medial system. For example, we do not know whether the lateral extensions ('wings') of the rostral rhomboid nucleus (Beckstead, 1984a) contribute to the striosome or the matrix projection. More generally, we do not know whether there is a clean break between the two systems or whether the cells are substantially intermingled. Analysis of this point in future studies by making small deposits of retrograde tracers in the striatum will be seriously hampered by the apparent medial system contribution to ventral matrix and medial strip tissue. It should be possible, though, to make small injections of anterograde tracers restricted to the central medial nucleus that would settle its affiliation. The central medial nucleus is of particular interest as most anatomists place it in the rostral intralaminar group (Rose, 1942; Murray, 1966). An analysis

of its compartmental targets in ventral caudate nucleus and the dorsal division of the nucleus accumbens should provide a principled basis for an assignment to either the medial or lateral systems. Interestingly, the chartings of a single autoradiographic case by Beckstead (1984a; case CRT-12) do suggest an anterior intralaminar-type fiber-patterning.

A specific projection to the medial nucleus accumbens that arises at least in part from the enlarged, anterior end of the paratenial nucleus was indicated by the findings from injections of the rostral pole of the thalamus. This is consistent with the retrograde evidence provided in the cat by Beckstead (1984a) and Groenewegen et al. (1980) (see also Swanson and Cowan, 1975; Kelley and Stinus, 1984). Given that these most anterior deposits produce labelling of the most medial part of the striatal complex, we could construe on topographic grounds that the rostral paratenial nucleus is also part of the medial thalamostriatal system. However, no conclusion on this issue is possible in the absence of projections to dorsal striatum or the dorsal division of the nucleus accumbens.

It should be emphasized that a thalamic projection to the ventral striatum does not assure a labelling of striosomes. Projections to the nucleus accumbens were labelled by deposits that predominantly labelled matrix tissue- in particular, in those involving the posterior intralaminar group. In addition, after injections of retrograde tracers into the nucleus accumbens (Groenewegen et al., 1980; Newman and Winans, 1980; Beckstead, 1984a; Jayaraman, 1985; Phillipson and Griffiths, 1985; Fuller et al., 1987; Christie et al., 1987), labelled cells in midline thalamus are present not only in the paraventricular and rhomboid nuclei, but also in the paratenial nucleus and the nucleus reuniens, neither of which may project to dorsal striatum, and in the central medial nucleus, which may participate in the projection to matrix tissue. It was, nevertheless, invariably the case that deposits in

the medial thalamostriatal system labelled the nucleus accumbens and the basolateral nucleus of the amygdala.

Fibers from the basolateral nucleus are known to project strongly into the ventral striatum (Krettek and Price, 1978a; Groenewegen et al., 1980; Kelley et al., 1982), and, as reported in Chapter 4, these fibers also selectively innervate striosomes in the medial and ventral caudate nucleus. Thus, the finding of the present report suggests that the joint afferentation of ventral and medial striosomes and the nucleus accumbens by basolateral nucleus may not be an incidental feature of the amygdaloid projections, but may reflect a strong functional linkage among these structures. The periventricular caudate nucleus ('medial strip') could be included among these structures on the grounds that this tissue is innervated by components of both the medial thalamic and basolateral nucleus projections. This ratification, by the innervation-pattern of medial thalamus, of an association among the basolateral nucleus and parts of the striatum should not be interpreted as indicating that the striatal connections of midline thalamus and the basolateral nucleus are equivalent. In fact, they differ markedly. The medial thalamostriatal system is not regionally restricted but has access to all districts parts of striatum, and, as far as we can determine, terminates within striosomes everywhere.

Our conclusion that the thalamic projection to striosomes also innervates the nucleus accumbens and amygdala is based on observations following large deposits of anterograde tracers. Support for this view comes from retrograde tracing studies on the afferent connections of the ventral striatum (Groenewegen et al., 1980; Beckstead, 1984a; Jayaraman, 1985) and the amygdala (Russchen, 1982b; Mehler et al., 1981; Ottersen and Ben-Ari, 1979). These reports all document projections to the nucleus accumbens and the amygdala by both the paraventricular and rhomboid nuclei. However, a firm conclusion of identical nuclear origin for these

projections is not yet warranted given the cytological and connectional heterogeneity to both thalamic nuclei. While retrograde labelling studies indicate that it is mainly the lateral (or posterior) division of the paraventricular nucleus that projects to the striatum (Macchi et al., 1984; Beckstead, 1984a), the subnuclear source of the thalamic projection to the amygdala has not yet been securely identified. Similarly, labelling of the rhomboid nucleus projection to the nucleus accumbens and the amygdala might allow for the interdigitation of different projection-neurons as this district sometimes (Groenewegen et al., 1980; Russchen, 1982b) (though not always- Fuller et al., 1987; Mehler et al., 1981) shows a discontinuous, or tiered, distribution of labelled neurons in coronal section. The possibility of a topographic segregation of medial thalamic cells projecting to dorsal and ventral striatum comparable to that that we have demonstrated in the projection to medial and lateral striatum appears, however, foreclosed by the broad distribution of retrogradely labelled cells seen in midline thalamus after tracer-deposits into ventral striatum (Groenewegen et al., 1980; Fuller et al., 1987).

Resolution of these issues will require double-labelling studies. The classic studies of thalamostriatal connections, however, suggest that the medial thalamostriatal projections might be branched, at least to dorsal and ventral striatum, and possibly to amygdala as well (Rose and Woolsey, 1943; Cowan and Powell, 1955; Powell and Cowan, 1954, 1956). Among the midline nuclear projections to the striatum, only those from the paratenial nucleus (to the nucleus accumbens) and from the central medial nucleus (to the medial caudate nucleus) could be demonstrated by partial destruction of the striatum. By contrast, the paraventricular and rhomboid nuclei only degenerated after more extensive forebrain damage. Powell and Cowan (1956) noted that the cases producing paraventricular nucleus damage had in common destruction of the lateral preoptic

area, but acknowledged that the "fibres [may] merely traverse this area to end elsewhere." A highly branched projection that is refractory to retrograde degeneration unless connections with all its terminal fields are interrupted (Rose and Woolsey, 1958), could account for the failure to demonstrate connections from the paraventricular nucleus to the dorsal striatum until the advent of modern axoplasmic tracing technologies.

There were two cases that presented striosomal labelling that we chose not to affiliate with the medial thalamostriatal system. In case CLRT-1R, in which a massive deposit was placed in ventromedial thalamus, the labelling of striosomes has a fibrous appearance unlike that seen in any of the midline deposits. Moreover, we were unable to establish that the observed projection arose from dorsal thalamus. In case CRTh-5R, in which a large deposit covered the dorsomedial thalamus caudally, nearly all of the labelled fibers were directed to matrix tissue and the examples of fibers filling striosomes were neither numerous nor particularly compelling. Clearly, more evidence would be required before we could conclude that there are additional dorsal thalamic sources of selective input to striosomes. It is instructive to note that the deposits in both of these cases (1) were situated in paramedian sites located just ventrolateral or dorsomedial to the midline complex and (2) elicited labelling of the ventral striatum and of the amygdala (though not selectively of the basolateral nucleus). Findings of retrograde tracing experiments of the afferent connections of the amygdala and ventral striatum (Mehler et al., 1981; Russchen, 1982b; Groenewegen et al., 1980; Beckstead, 1984a) suggest that further study of this issue might profit from examining, with more restricted tracer-deposits, the connections of the ventral nucleus reuniens and the tissue abutting the habenular complex.

Functional considerations. The midline position of the thalamic

striosome-projecting system may be important to its function. In the cat, the massa intermedia is quite prominent and the midline nuclei are known to project bilaterally to striatum (Jayaraman, 1985; Groenewegen et al., 1980). Consequently, even if individual cells do not project to both striata (Takada et al., 1987), neurons projecting to each striatum are intermingled and are set to receive, as interstitial nuclei of thalamic commissural connections and extrathalamic afferent fibers passing contralaterally (Gurdjian, 1927; Scheibel and Scheibel, 1967), a near balanced input from the two sides of the brain. The striosome system of the cat's dorsal striatum (and the ventral striatum and basolateral nucleus of the amygdala as well) thereby appear positioned to be bilaterally modulated by a direct and coordinate mechanism that is largely denied to the extrastriosomal matrix tissue of the dorsal striatum.

A system of bilateral control could also participate in the transfer of effects from one side of the brain to the other. Glowinski and colleagues have found that a number of *unilateral* manipulations in the cat, most notably delivery of the drugs α-methylparatyrosine and d-amphetamine to the substantia nigra, produce bilateral, asymmetric changes in the measured release of dopamine in both the substantia nigra and the caudate nucleus (Cheramy et al., 1981, 1983; Leviel et al., 1981). Cheramy et al. (1981) established that the asymmetrical, contralateral response to the unilateral manipulation of the dopamine system could be nearly abolished by sagittal section of the thalamus and overlying corpus callosum, but not by sagittal sections made rostral or caudal to the thalamus (see also Leviel et al., 1981). This sectioning of the massa intermedia would have several effects, including interruption of bilateral projections from the reticular nucleus to the basal ganglia-afferented nuclei of the thalamus (Rinvik, 1984; Herkenham, 1986), but prominent among them would be a lateralization of the input-output

connections of what striatally-projecting midline neurons actually survive the transection. This possibility, of midline nuclear mediation of bilateral regulation of dopamine release, could be tested with lesions produced with fiber-sparing neurotoxins.

Given that the size of the massa intermedia varies both across and within species, and that it is sometimes nearly absent (Ariens Kappers et al., 1936; Crosby et al., 1961, 1967), (Ariens Kappers et al., 1960; Crosby et al., 1962; Crosby et al., 1967) it seems unlikely that the primary role of the thalamic projection to striosomes is to carry out bilateral modulation of basal ganglia activity. In a species such as the cat, though, it might be informative to test for the participation of the medial thalamostriatal system in behaviors requiring coordinate activation of the extrapyramidal system. A starting point for such inquiry might be the finding of MacDonnell and Flynn (1964) in the cat that predatory (quiet-bite) attack on rats, when the rat is placed in the cat's field of view, can be elicited by electrical stimulation of midline thalamus.

The lateral thalamostriatal systems

Herkenham and Pert (1981) reported that projections from the parafascicular nucleus of the thalamus innervate matrix tissue and avoid AChE-poor striosomes in the lateral caudatoputamen of the rat. We have confirmed this finding in the cat for the full posterior intralaminar complex and have, in addition, found that the anterior intralaminar nuclei and large parts of the lateral thalamic mass, including the ventral nuclear complex, also project to matrix tissue. These findings have led us to a general conclusion about the thalamostriatal connection, that lateral thalamostriatal projections are primarily to the matrix compartment.

The lateral thalamostriatal projection-systems identified here do not innervate matrix tissue in the same manner. Deposits placed in the ventral nuclear

complex elicited fibrous labelling that was inhomogeneously distributed in the matrix, deposits situated in anterior intralaminar nuclei produced a smooth, homogeneous diffusion of grains in the matrix, and deposits placed in posterior intralaminar nuclei led to a variety of patterns of striatal labelling, including elements of both the diffuse anterior intralaminar and the fibrous rostral ventral complex types of innervation. Given that the nuclei in each of these complexes are contiguous and show a near-complete topographic coverage in their projection to the striatum, this evidence for different patterns of matrix innervation argues strongly for the presence of at least three distinct projection-systems within the lateral thalamostriatal connection.

For two of these systems- those arising in the posterior intralaminar and ventral nuclear complexes- and also for parts of the posterior thalamic projection, there was evidence for inhomogeneity in the innervation of matrix tissue throughout the caudate nucleus (see Fig. 5-6B). A mosaic organization for the projection from somatic sensory cortex to matrix tissue in the dorsolateral caudate nucleus was previously described by Malach and Graybiel (1986). These workers found, by double-labelling techniques, that at least part of the patchiness of the projection to matrix could be accounted for by segregation of afferent fibers according to the submodality of the cortical area from which they issued (areas SI and 3a). We did not attempt any such experiments to probe the organization of the matrix mosaicism suggested by our thalamic experiments; but the finding that large injection sites or prolonged exposure times could reduce or obliterate the heterogeneities seen in the posterior intralaminar or ventral nuclear complex projections suggests that if there are separate thalamic zones that interdigitate in their projections to striatal matrix, they are situated close to one another.

For the posterior intralaminar nuclei, the possibility of subdivisions within

the projection-system was particularly acute given the variety of patterns of innervation we saw across the cases; we were, however, unable to construct a simple, coherent account of these shifts. Interestingly, Royce and Mourey (1985), in a study of CM-Pf efferent connections, reported that their rostral and caudodorsal deposits produced marked cortical labelling, while their caudoventral ones did not. We saw a similar arrangement in our cases (see also Nauta and Whitlock, 1954; Herkenham, 1978). And although it seemed quite likely that what was special about the caudoventral deposits was that they did not encroach on adjacent parts of dorsal thalamus, the possibility of significant compartmentation in the posterior intralaminar complex deserves further study.

The lateral posterior thalamus, and mainly the LM-Sg complex, is a significant source of striatal input, but was only partially explored in these experiments. Our data indicated a projection primarily to matrix tissue from this thalamic district, but this conclusion needs more experimental support. Our case-material was not extensive enough to show a common pattern of matrix innervation for this part of thalamus or to establish a complete topography for the connection. While it seems likely that this part of thalamus composes a fourth lateral thalamostriatal system, the possibility that it is a posterior component of one of the other projection-systems can not be excluded.

Topographic organization of thalamostriatal projections

The medial and lateral thalamostriatal systems are distinguished by the compartmental targets of their fibers, but the differences in their topographic organization are perhaps just as fundamental. Every deposit labelling the medial system also labelled a near-complete longitudinal slice through the full height and length of the striatum. As a result, this projection is spatially organized only across the mediolateral dimension in the striatum. By contrast, the innervation of

matrix tissue by the lateral systems is much less sweeping and so they are free to range in both the mediolateral and dorsoventral axes. Thus, the thalamic projection to striosomes is distinguished from that to matrix by an obligation to link, by conjoint innervation, broad stretches of the striatum.

The linkages made by the medial thalamostriatal connection- of striosomes, ventral matrix tissue and ventral striatum across a parasagittal slice of striatum- are in accord with those noted in studies of other striatal afferent systems. As reviewed earlier, the basolateral nucleus of the amygdala innervates ventral striatum and striosomes in ventral and medial caudate nucleus. The thalamic data extend this linkage of ventral striatum and striosomes to include striosomes throughout the striatum. The observation that the thalamic projection to striosomes reaches ventral, but not dorsal, matrix tissue fits with some of our findings on the corticostriatal connection: when cortical regions show a bi-compartmental pattern of projection, it is organized as an innervation of matrix tissue *ventrally* and striosomes dorsally within its striatal field of termination (see Chapter 6). Interestingly, this finding that the corticostriatal projection is highly organized (and sometimes extended) in the dorsoventral dimension agrees with a parcellation of the striatum into mediolaterally arrayed longitudinal domains. Such an analysis is not original to us, but has been put forward previously in studies of the corticostriatal connection, most notably that of Selemon and Goldman-Rakic (1985) in the monkey. What is novel in our medial thalamostriatal data is the suggestion that the domains span the full dorsoventral dimension of the striatum. To make this point concrete, the medial thalamic projection to the lateral striatum would suggest a link between the dorsolateral striatum (sensory motor-recipient sector) and the lateralmost part of the ventral striatum. More evidence will be needed before we can conclude that such a longitudinal 'slice' arrangement

is an authentic organizational principle underlying the disposition of striatal afferent connections.

The medial and lateral systems not only differ in their general plans of topographic organization, but also in their specific connectional topographies. The lateral thalamostriatal systems we, and others, have examined are all similar in having a topography that preserves, with small gyrations, mediolateral and dorsoventral relationships (Powell and Cowan, 1956; Herkenham, 1978a; van der Kooy, 1979; Beckstead, 1984a). In the medial thalamostriatal system, however, the mediolateral axis of the striatal terminal fields arises by a 90° rotation of the anteroposterior axis in the thalamic zone of origin. There was no evidence in our cases for any sequestration of the medial system-projection in the anterior-posterior dimension of the striatum. This was not surprising as most striatal afferent projections are elongated in this dimension (Goldman and Nauta, 1977; Beckstead, 1984a; Beckstead et al., 1979; Jimenez-Castellanos and Graybiel, 1987). In fact, when there is an organization in this axis in the disposition of afferent connections, it tends to be a rough division into projections favoring the rostral two-thirds of the striatum and those favoring the caudal third (Yeterian and Van Hoesen, 1978; see Chapter 6). In our thalamic material, such anterior-posterior segregation was clearly observed only after deposits in the posterior intralaminar complex and in the lateral nuclear mass. In these examples, projections to rostral striatum arose from more anterior thalamic deposits and those to caudal striatum issued from more posterior thalamic injection sites, which is consistent with projections of the lateral system maintaining an anteroposterior axis as well (cf. Beckstead, 1984a).

Our conclusions on medial thalamostriatal system topography are supported by a retrospective examination of maps of thalamostriatal neurons: labelling in rostral midline nuclei is prominent after medial striatal deposits of retrograde

tracers (Beckstead, 1984a; Jayaraman, 1985), while caudal labelling in the paraventricular and rhomboid nuclei predominates after injections of the dorsolateral caudate nucleus and putamen (Royce, 1983a; Beckstead, 1984a; Jayaraman, 1985- note "dorsal division of the parafascicular nucleus"; Takada et al., 1985b; Hu and Jayaraman, 1986; C. Olson, personal communication). Interestingly, this review of the retrograde labelling data, by accounting for the previously unexplained 'scatter' of cell-labelling often seen in the midline nuclei (Beckstead, 1984a; Jayaraman, 1985), to some extent 'cleans up' the evidence for spatial organization in the thalamostriatal system.

Beckstead (1984a) has argued that the striatopetal cells encircling the mediodorsal nucleus[7] should be considered together because, as a group, they exhibit a topographically coherent projection that reaches all parts of the striatum (see Beckstead, 1984a; Fig. 28). Our evidence that the medial and lateral components of this ring have different compartmental targets in the striatum and participate in fundamentally different projection-systems, undermines this analysis. However, the *pattern* of retrogradely labelled cells observed by Beckstead (1984a) is what we would expect. First, the nuclei of the anterior intralaminar complex do present a topographic projection to the striatum that roughly maintains mediolateral and dorsoventral relationships (this report; Powell and Cowan, 1956; Herkenham, 1978; van der Kooy, 1979). Second, an injection of retrograde tracer into medial caudate nucleus should label the medial thalamostriatal system at rostral thalamic levels where the 'ring' of striatally projecting cells is most conspicuous. While lateral caudate nucleus deposits would also elicit midline labelling, this would occur only at more caudal thalamic levels. Thus, an analysis of

[7]His rostral intralaminar complex- which includes the central lateral, paracentral, central medial and rhomboid nuclei; that is, essentially the central commissural system of Rose (1942)- plus the paraventricular nucleus and the para-stria medullaris zone

thalamostriatal connections incognizant of the compartmental organization of the projection should produce precisely the interpretation of Beckstead (1984a).

Developmental considerations. The positioning and topographical organization of the medial and lateral thalamostriatal systems may be distinguished in development. From thymidine-incorporation studies of neurogenesis it has been established that the laterally situated cells of the dorsal thalamus are born earlier than more medially placed ones (Angevine, 1970; Fernandez and Hermes, 1973; McAllister and Das, 1977; Altman and Bayer, 1979a) and Altman and Bayer (1979b) have presented circumstantial evidence that the germinal eminence of the anteromedial and midline cell-groups may be physically separate from those of older, more laterally resident thalamic districts. A late birth for the medial thalamostriatal cells does not shadow the developmental sequence in the striatum as neurons destined for the striosomal compartment are made early (Graybiel and Hickey, 1982; van der Kooy and Fishell, 1987). However, histogenetic gradients may be used in more covert ways in establishing the thalamostriatal connection. It is known that striatum, like thalamus, is born in an 'outside-in' sequence (Angevine and McConnell, 1974; Fentress et al., 1981) which, given a lateral thalamostriatal projection-system that preserves lateral-to-medial topography, suggests a coordinate connection that observes relative birthdate. Obviously a lateromedial histogenetic gradient could not distinguish among parts of the medial thalamostriatal system. There is, however, a caudorostral gradient in thalamic cell-birth whereby older cells are situated more posteriorly (Angevine, 1970; Fernandez and Hermes, 1973; McAllister and Das, 1977; Altman and Bayer, 1979a). Given our findings on the topography of the medial thalamostriatal projection, it would appear that an arrangement of older source cells reaching older (and more lateral) striatal target neurons holds for this system also.

Afferent circuitry of the thalamostriatal connection

Two important conclusions flow from a review of the afferent connections of thalamostriatal nuclei: 1) the hindbrain and spinal cord may have near immediate access to the striosome system through the agency of the medial thalamostriatal system; and 2) the medial and lateral thalamostriatal systems receive considerably different input.

The intralaminar nuclei and the midline are principal thalamic targets of ascending connections from the brainstem reticular formation (Nauta and Kuypers, 1958; Basbaum et al., 1976; Edwards and de Olmos, 1976; Graybiel, 1977b; Saper and Loewy, 1980; Jones and Yang, 1985; Vertes et al., 1986) and the spinal cord (Mantyh, 1983a; Craig and Burton, 1985). Deposits of anterograde tracers in brainstem indicate that, while the medial and lateral systems share input from some zones, such as the central gray substance and adjacent mesencephalic tegmentum (Chi, 1970; Mantyh, 1983b; Edwards and de Olmos, 1976), many structures are more selective in their innervation of the two systems. For example, the intralaminar nuclei are strongly favored by pathways arising in parts of the paramedian pontine and gigantocellular medullary reticular formations (Graybiel, 1977b; Robertson and Feiner, 1982; Zemlan et al., 1984; Jones and Yang, 1985; Vertes et al., 1986), whereas the paraventricular nucleus is apparently the sole thalamic target of fibers issuing from the region of the nucleus of the solitary tract (Ricardo and Koh, 1978). The thalamic projections of the hypothalamus are perhaps the most telling about these differences in input; a number of its constituents, including the anterior hypothalamic area, the ventromedial nucleus, the lateral hypothalamic area and the preoptic regions, project selectively to midline nuclei (Conrad and Pfaff, 1976a,b; Saper et al., 1976, 1978, 1979a,b; Swanson, 1976). By contrast, the intralaminar (including the central medial

nucleus) and ventral nuclear complexes, but not the paraventricular and rhomboid nuclei, are targets for fibers from cerebellum, tectum and pretectum (Sugimoto et al., 1981; Hendry et al., 1979; Graham, 1977; Harting et al., 1980; Berman, 1977; Nakano et al., 1985; Kaitz and Robertson, 1981). Thus, the medial system can be characterized by its affiliations with the 'limbic system', in the broadest sense of the term (Nauta, 1958), while the lateral system is distinguished by its exclusive links with many brainstem 'extrapyramidal' structures. Interestingly, this exclusivity does not appear to extend to the basal ganglia themselves. There is anterograde evidence for pallidal and nigral input not only to the ventroanterior and ventromedial nuclei and the CM-Pf complex, but to all sources of thalamostriatal neurons, including, apparently, the paraventricular nucleus (Nauta, 1979; Hendry et al., 1979; Takada et al., 1984; Sugimoto and Hattori, 1984; van der Kooy and Kolb, 1985).

This distinction between the sources of inputs to the medial and lateral systems extends to the fiber-tracts over which these inputs principally travel: the intralaminar nuclei are reached by the dorsal thalamic branch of Forel's central tegmental tract; the midline nuclei, by the dorsal longitudinal fasciculus of Schutz (Nauta and Kuypers, 1958). The association of the midline nuclei (and, in particular, the paraventricular nucleus) with the dorsal longitudinal fasciculus is noteworthy in two respects. First, this fiber system is distinguished from all other thalamic fiber-tracts by its rich and diverse content of neurotransmitter substances, including norepinephrine, serotonin and peptides such as corticotropin, neuropeptide Y and atrial natriuretic peptide (Fuxe, 1965; Lindvall et al., 1974; Swanson and Hartman, 1975; Steinbusch, 1982; Bobillier et al., 1975; Azmitia and Segal, 1978; Parent et al., 1981; Pilcher and Joseph, 1984; Chronwall et al., 1985; Standaert et al., 1986). Second, many of the afferent nuclei of midline thalamus

are, in fact, distributed along the course of the dorsal longitudinal fasciculus. According to a retrograde tracing study by Cornwall et al. (1985), these nuclei show a clear rostrocaudal topography in their projections to midline thalamus whereby central gray substance and hypothalamic inputs favor, respectively, the caudal and rostral paraventricular nucleus of the thalamus. This finding, assuming that it is not due to a fibers-of-passage complication, would suggest that central gray tissue, and not hypothalamus, is positioned to exercise control over striosomes in the lateral, sensory motor-recipient district of the striatum.

Although topographic organization within the central tegmental tract has been proposed, it has never been satisfactorily demonstrated (Nauta and Kuypers, 1958; Edwards and de Olmos, 1976). If present, it would suggest a simple explanation as to why the lateral thalamostriatal systems have roughly similar topographies; that is, because major inputs to these nuclei are conveyed over the same fiber-system. Also arranged to take advantage of this shared topographic structuring may be the intrathalamic connections of the posterior intralaminar complex, which are directed rostrally to the anterior intralaminar and ventral nuclei (Nauta and Whitlock, 1954).

Some aspects of the anatomy of thalamostriatal and thalamocortical connections

Parallel structuring. The thalamostriatal connection is a complete one in the sense that it reaches both striatal compartments throughout the dorsal striatum. It achieves this by multiple projection-systems, each with a distinct pattern of innervation and topography. This arrangement is in keeping with that of the thalamic connection with the cortex as this also consists of multiple projection-systems, distinguished by lamination pattern and spatial organization (Herkenham, 1986; Macchi, 1983). Presumably, there are more thalamocortical systems than

there are thalamostriatal ones, but it is not clear how much the two classes of thalamic efferents differ qualitatively. For example, according to retrograde labelling experiments, cortical projections from individual thalamic nuclei appear to be further specified by particular cell-types connecting with particular cortical layers (Diamond, 1983). Although almost impossible to test for with retrograde tracer-deposits into the striatum, a similar arrangement could well account for the heterogeneity we saw in the pattern of matrix projection from the CM-Pf complex.

One respect in which the cortical and striatal connections are different is that at least some thalamic nuclei show area-dependent lamination patterns in their projection to cortex (Herkenham, 1980; Berson, 1980). Although in some cases we did see different compartmental patterns in different regions of the striatum, these were all analyzed as due to injection site involvement of more than one projection-system. This absence of significant region-dependent variations in the pattern of striatal innervation from single sources in thalamus may be due not to a fundamental difference between the thalamocortical and thalamostriatal systems, but to the nature of the cortex. Unlike striatum, cortex has extensive associational connections and these are organized in part according to principals of hierarchy and progressivity across cortical areas (Rockland and Pandya, 1979; Maunsell and Van Essen, 1983; Jones and Powell, 1970; Barbas, 1986) and the area-dependent lamination pattern seen in the thalamocortical connection appears to be a reflection of this cortical organization. Interestingly, the corticostriatal projections *do* show regional variations in their compartmental pattern of striatal termination: tracer-deposits placed in many regions of cat cortex elicit a pattern of filling striosomes dorsally and avoiding them ventrally in their striatal field of termination (see Chapter 6). The reason the thalamostriatal projection appears 'impoverished' in their complexity may be simply that they do not involve the cortex.

Coordinate disposition. Thalamocortical neurons are present, apparently, in every dorsal thalamic nucleus that projects to the striatum and thalamic cells in the anterior intralaminar and ventral complex nuclei (and, more sporadically, in the rhomboid nucleus and posterior intralaminar nuclei) have been shown by anatomical methods to send collaterals to both cortex and striatum (Royce, 1983; Macchi et al., 1984). The question naturally arises whether, and in what way, thalamocortical and thalamostriatal projection-systems are coordinated when they occur together. The corticostriatal system is one key to analyzing such coordination.

Corticostriatal projections are both topographically and compartmentally organized. Thus, the question of coordination can be posed as whether, for a given thalamic zone, its indirect thalamo-cortico-striatal connections reach the same striatal district and compartment as its direct thalamostriatal connection. To take an example from the posterior thalamus, where these relationships appear orderly: both the medial division of the posterior nuclear group (Beckstead, 1984b; this report) and at least one of this thalamic nuclei's main cortical targets, area SIII (Malach and Graybiel, 1986; Tanji et al., 1978; Garraghty et al., 1987), project to the matrix compartment of the dorsolateral caudate nucleus and putamen (somatic sensory-recipient sector of the striatum).

Our best evidence for topographic orderliness of direct and indirect thalamostriatal connections comes from the group of cases with injection sites in the ventral nuclear complex. As reported in the rat (Herkenham, 1979; Herkenham, 1986), fibers from this part of thalamus are distributed to layer 1 across a broad expanse of cortex, but, in addition, accumulate in deeper layers in more restricted cortical districts. For medial ventroanterior nucleus injection sites, the more restricted projection-field includes medial area 6 (along the lip of the ventral bank

of the cruciate sulcus) stretching rostrally to the dorsal half of the gyrus proreus and caudally towards area 24. The striatal projections of these cortical areas are by no means coextensive, but they do overlap (cf. Yeterian and Van Hoesen, 1978). The region of overlap of their strongest projections to striatum is in the dorsomedial and central caudate nucleus (see Chapter 6) and this was the district of striatum labelled after deposits into the medial ventroanterior nucleus. A parallel pattern of intersecting direct and indirect striatal targets was seen in our deposits in lateral ventral complex (labelling premotor and motor cortices and dorsolateral caudate nucleus and dorsal putamen) and in the ventromedial nucleus (labelling insula cortex, *inter alia*, and ventrolateral caudate nucleus). A roughly similar arrangement was noted in matching and comparing our anterior intralaminar cases with our cortical deposits, but the data were less compelling, in part because of the significant injection site involvement of adjacent, non-striatally projecting nuclei of the dorsal thalamus.

Both the posterior intralaminar complex and midline nuclei project to cortex (Jones and Leavitt, 1974; Wyss et al., 1979). We could, though, draw no conclusions from our autoradiographic data because the connections are not strong ones and because the cortex labelling we observed in the relevant cases could not be safely assigned to these nuclei rather than to adjoining thalamic districts, such as the mediodorsal nucleus, with more robust cortical projections. At least for the posterior intralaminar nuclei, though, its afferent projections *from* cortex are organized so that the indirect cortico-thalamo-striatal projection reaches the same striatal district as does the direct corticostriatal one (Powell and Cowan, 1967). The situation is least clear for the medial thalamostriatal system. If the cortical connections of the rhomboid nucleus (which appears to have a larger thalamocortical projection than does the paraventricular nucleus) do reflect the

topography of its striatal connections, the arrangement we would expect is for cells of the rhomboid nucleus that project to the medial limbic cortex (which in turn projects to medial caudate nucleus-see Chapter 6) to lie rostral to neurons projecting to sensory-motor cortex. Published reports offer some support for this suggestion (Kaitz and Robertson, 1981; Royce, 1983), but direct examination of the point is required.

Assessing whether there is congruence of direct and indirect thalamocortical projections at the compartmental level is more difficult. Evidence of congruence clearly would be that the cortical targets of the medial and lateral thalamostriatal systems differ in appropriate ways in their affiliations with striosomes and matrix. The problems here are, first, that we do not know what the cortical targets of the medial system are. This is not just a technical issue; it is not established whether projections from midline to cortex are at all spatially selective. Second, even if there were identified cortical targets for the medial and lateral systems, it is unclear what kind of orderliness could be extracted given that many of the cortical regions that innervate striosomes also, apparently, provide a significant projection to matrix tissue. The difficulties this arrangement causes are illustrated by the otherwise orderly connections of the ventromedial nucleus of the ventral complex. Its most prominent cortical target is insular cortex, which projects heavily to the matrix of the ventrolateral caudate nucleus (the direct target of the ventromedial nucleus). However, insula cortex also projects more dorsally in caudate nucleus, where it selectively reaches striosomes; in fact, it provides the most widespread innervation of striosomes of any cortical area we have examined (see Chapter 6).

There may, however, be a deeper principle at work. In the ventral nuclear complex, the ventro*medial* nucleus projects to the cortex with the most extensive access to striosomes. Similarly, for cortical areas reached fibers from the

mediodorsal nucleus and the posterior thalamus, the areas projecting to striosomes have more medially situated thalamic connections than areas projecting principally or solely to matrix tissue (see Chapter 6). These observations suggest that a lateral-medial difference might control trans-cortical access to striosomes. Such an arrangement is reminiscent of the lateral-to-medial, band-like organization that describes the topography of thalamocortical connections in the monkey (Kievit and Kuypers, 1977). Our suggestion here is that a lateromedial shift might act independently on different aspects of thalamic efferent relationships, including their access to the striosomal system. For the thalamo-cortico-striatal connection, where the intercalated corticostriatal system is quite complex in its compartmental organization, the lateromedial difference appears to operate as a gradient across thalamocortical nuclei. For the direct thalamostriatal connection, the lateromedial distinction is simple and, in fact, dichotomous.

As we have noted, the territories that give rise to the medial thalamostriatal system also project to ventral striatum and to the amygdala, but amygdalar and ventral striatal connections are not restricted to this system. These additional efferent connections, however, appear to arise exclusively from relatively medial thalamic sites, such as para-midline thalamus, and from nuclear regions such as the LM-Sg complex that lie along the meso-diencephalic border (see above; Groenewegen et al., 1980; Russchen, 1982). Thus, the lateral-to-medial gradient that predicts affiliations with striosomes may represent a general constraint on thalamus, one expressed in the disposition of all thalamic forebrain projections.

Prospects for analysis of function in the thalamostriatal system

The principal cell-type of the striatum, accounting for from 70% to 95% of the neurons depending on the species examined, is a medium-sized cell that is densely covered with spines along all but the most proximal part of its dendrites

(Kemp and Powell, 1971a; DiFiglia and Graveland, 1983). Thalamic and cortical projections to the striatum, when viewed according to the anatomy of this cell, appear remarkably equivalent. Both inputs terminate on spines and both are excitatory (Kemp and Powell, 1971b; Kitai et al., 1976a). From the evidence of retrograde labelling studies employing the D-aspartate uptake mechanism, they appear to use similar or identical neurotransmitters (Streit, 1980; Fuller et al., 1987; Christie et al., 1987). This equivalence extends to the level of single cells: not only do thalamus and cortex converge on individual neurons, but their terminals appear to be interdigitated along the dendrites in a regular and even fashion (Kemp and Powell, 1971c). These observations indicate a structurally similar status for the two principal exogenous inputs to striatum and suggest that the systems may be able to substitute for each other functionally. Such a possibility would limit behavioral approaches to differential processing between striosomes and matrix that relie on lesions in just one of thalamus or cortex. There are, of course, many problems with such experiments- the cortical origins of input to striosomes is too widespread to permit any sensible interpretation of its destruction; and any injury to thalamus of sufficient size to remove one of the projection-systems would damage unrelated components of the thalamocortical system.

Attempts to probe the physiology of the relationship between striosomes and matrix may not, however, be limited to single-unit studies or hopes for a pharmacological or molecular 'magic bullet'. Animals whose neocortex was removed at birth exhibit a range of complex behaviors (Murphy et al., 1981). In such animals, both the inputs and the projections of the thalamostriatal system should remain largely intact (Walker, 1938; Powell, 1952; Powell and Cowan, 1967; see also Krauthamer, 1979). Behavioral experiments could then take advantage of the spatial segregation of the thalamostriatal system into medial and lateral

components to probe differential effects of depriving either striosomes or matrix of exogenous input. As destruction of the medial system would compromise input not just to striosomes in dorsal striatum, but also to ventral striatum and the basolateral nucleus of the amygdala, care would need to be taken in its interpretation. This should not hinder inquiry given, on the one hand, the apparent functional linkage of these other structures to the striosome system and, on the other, the fact that such lesions would not disrupt ascending input to much of the amygdala and would not fully disconnect the ventral striatum from thalamus. It is possible that behavioral study of the thalamostriatal system that exploits the anatomy outlined in this report may offer genuine insight for guiding a functional analysis of the compartmental organization of the striatum.

Chapter 6

The Corticostriatal Connection

Anterograde degeneration studies employing silver impregnation techniques not only provided the first credible experimental evidence for a projection from cortex to striatum (Glees, 1944; Nauta, 1953); they also offered a comprehensive description of the organization of the pathway (Webster, 1961, 1965; Carman et al., 1963, 1965; Kemp and Powell, 1970): First, essentially all regions of cortex project to the striatum and all parts of striatum receive input from cortex (Webster, 1961; Carman et al., 1963). Second, lesions in individual cortical areas produce well-marked zones of degeneration in the striatum (Carman et al., 1963). Third, certain features of the projection, such as its intensity, vary with the functional region of cortex examined. For example, the volume of the connection from frontal cortex is much greater than that from visual cortex . Fourth, the striatal district of destination for a cortical area is in large part determined by a global topography: roughly put, given regions of cortex tend to project to nearby regions of the striatum. Because striatal degeneration from cortical damage typically extends as "a band ... orientated dorsoventrally" (Kemp and Powell, 1970), this organizational principle is most apparent in the mediolateral and anteroposterior dimensions (Webster, 1961; Carman et al., 1963). Fifth, within this topography, there is opportunity for overlap in the termination of projections from different cortical areas. For example, somatic sensory and motor cortices in the monkey appear to project to the same striatal territory (Kemp and Powell, 1970).

To a large degree, these conclusions about the organization of the connection have been confirmed with the autoradiographic method for tracing neural

pathways. The principal revision has been that the topography of the projection is not strongly organized in the anteroposterior dimension: deposits in prefrontal cortex elicit labelling not only in head of the caudate nucleus, but also in its body and tail (Goldman and Nauta, 1977; Selemon and Goldman-Rakic, 1985); and deposits in temporal cortex produce labelling not only in the tail of the caudate nucleus, but also in its head (Yeterian and Van Hoesen, 1978; Van Hoesen et al., 1981). This finding of an expanded distribution to the projection suggests a greater overlap among cortical areas in their striatal fields of termination than was previously suspected. Yeterian and Van Hoesen (1978) have proposed that at least some of this overlap is governed by a principle of "cortical areas related via reciprocal cortico-cortical connections project[ing], in part, to similar areas within the caudate nucleus."

The modern technologies of anterograde tracing has also demonstrated much that is novel about the organization of the corticostriatal connection. Principal among these is the observation that cortical fibers, within their striatal field of termination, are not homogeneously distributed, but are arranged as patches (Kunzle, 1975; Kunzle, 1977; Kalil, 1978; Kunzle and Akert, 1977; Goldman and Nauta, 1977; Jones et al., 1977; Wise and Jones, 1977; Yeterian and Van Hoesen, 1978; Van Hoesen et al., 1981; Selemon and Goldman-Rakic, 1985). Graybiel and I found that, at least for the frontostriatal projection in the cat, most of the inhomogeneities observed could be accounted for by cortical fibers respecting the boundaries of histochemically defined striatal tissue-compartments: in tissue sections taken through the striatum and prepared for acetylcholinesterase (AChE) histochemistry, there are circumscribed zones of reduced staining regularly distributed in a more densely stained matrix tissue (Graybiel and Ragsdale, 1978b) and, following tracer-deposits in cat frontal cortex, labelled fibers are

observed to innervate the enzyme-poor zones in dorsal caudate nucleus and avoid them in ventral caudate nucleus (Ragsdale and Graybiel, 1979, 1981). These AChE-poor zones, designated striosomes, are now known to be a characteristic feature of mammalian striatum. They are seen not only after AChE staining, but, as has been documented in a number of correlative studies, are displayed by most histochemical preparations that localize neurochemicals. Furthermore, the tissue-compartments established by the histochemistry are observed not only by striatal afferent fibers from the cortex, but also by inputs from the thalamus, substantia nigra and amygdala, and by the distributions of striatal projection cells (see chapter 2).

Following our initial report on the compartmental organization of the corticostriatal connection, Donoghue and Herkenham (1986) examined in the rat the distribution of corticostriatal fibers with respect to zones enriched in opiate ligand binding sites (which are known to correspond to AChE-poor striosomes in this species; Herkenham and Pert, 1981). They confirmed a projection from frontal cortex to the striosomal compartment and reported that the matrix compartment is the principal target of fibers from anterior cingulate cortex and from primary visual, somatic sensory and motor cortices (see also Gerfen, 1984; Ragsdale and Graybiel, 1984; Malach and Graybiel, 1986). In discussing their findings, Donoghue and Herkenham raised the possibility that all cortical projections to striosomes may originate from the prelimbic cortex (cortical area 32). Such an outcome, that the cortical innervation of striosomes is not topographically specified and arises in a single area, would be of great importance, not the least reason being that it would enable behavioral studies of the consequences of disconnecting striosomes from all cortical input. Clearly, a range of cortical areas needs to be surveyed. This is required not only to identify or exclude other possible sources of striosomal

afferentation; given the recent evidence from a study of cat somatic sensory cortex that there can be clear inhomogeneities in striatal fiber-patternings that can not be accounted for by striosomal compartmentation (Malach and Graybiel, 1986), it is important to test more completely the relationship between cortical projections and striatal compartments. We chose the cat for these experiments because it has a large reserve of accessible, well-characterized association cortex and, presumably, it is in the association cortices that additional striosomal input is most likely to be found.

There should be other important dividends to a full review of corticostriatal projections. First, the functional role of striatal compartmentalization is completely obscure. But, whatever it is, it must be latent in the differential input to the two compartments. One approach to this issue is to identify those features of an input that determine whether it affiliates with striosomes or matrix in its striatal field of termination. Only the cortex, with its range of functionally specified areas nearly all of which project to the striatum, is rich enough to favor such an analysis.

Second, conclusions from degeneration studies about the organization of the corticostriatal projection have led some workers to propose that cortical inputs mark out separate districts in striatum which in turn establish parallel channels through basal ganglia circuitry (Johnson et al., 1968; Johnson and Rosvold, 1971; Alexander et al., 1986; Jeffers and Olson, 1985). One serious difficulty with this scenario is that we have no full account of corticostriatal topography, based on modern tracing methods, to succeed that based on degeneration techniques. For example, if the principle outlined by Yeterian and Van Hoesen (1978), of transcortically linked areas having common striatal targets, were to hold for the progressive sequence of transcortical connections described by Jones and Powell (1970), there would be ample opportunity for convergence across basal ganglia

'channels' by partial overlap of cortical inputs in the striatum. Although some might argue that partial overlap, unless quite extensive, is of little functional significance and only reflects the presence of regions of transition, a finding that overlapping inputs are highly organized- for instance, that they interdigitate with each other along compartmental lines- would suggest the operation of specific mechanisms of convergence.

Results

Deposits of anterograde tracing substances were made throughout the neocortex. In every case, labelled fibers were traced to the ipsilateral striatum, where they were distributed inhomogeneously. In most experiments, we were able to determine the relationship between the patternings seen in the anterograde labelling and the distribution of striosomes demonstrated histochemically in serially adjoining sections.

The results of our analysis are presented in three parts. First, we consider together the projections of parietal and cingulate cortex because they provide the bulk of the association cortex input to striatum that was found to avoid striosomes and innervate matrix tissue. Second, we present our observations on the connections of frontal, insular and rostral temporal cortex- regions which are linked in providing cortical input to striosomes. We also review the striatal projections of motor cortex. In a preliminary report on the striosomal organization of corticostriatal projections in the cat, we had observed that single injection sites in frontal cortex elicit a dual pattern of compartmental innervation in the striatum (Ragsdale and Graybiel, 1981; see above). It was unclear, though, whether this pattern is a feature of single cortical areas or reflected experimental involvement of more than one cortical field. In this report we present evidence supporting the view that regions of frontal cortex do participate in multiple patterns of compartmental

affiliation. Third, we examine the distribution of fibers from caudal temporal cortex and from cortical areas participating in early and late stages of sensory processing. We also note our limited findings on projections from perirhinal and entorhinal areas. We collect these cases because they are thematically related and because several of them show inhomogeneous striatal labelling that either is independent of the histochemical compartmentalization or can not be satisfactorily related to it.

Cortical projections to the striatum differ not only in their compartmental specification, but also in their topographic organization. Figure 4-1 was prepared to ease the description of the spatial distribution of labelled fibers seen in our cases. It depicts the arrangement of label in the cat's striatum after deposits of tracer into pericruciate and posterior parietal cortex and into the amygdala (Fig. 4-1C,D,A). As reviewed in chapter 4, the striatal domains of these projections are non-overlapping (Fig. 4-1). In line with previous observations on the corticostriatal projection (see above), we found that in almost every case striatal labelling was elongated in the anteroposterior dimension and that in many cases it extended from the head of the caudate nucleus through the body. In selected cases, though, labelling was more pronounced in, or even fully restricted to, either the anterior two-third's or the posterior one-third of the striatum. This more restricted labelling was most clearly seen in the projections to the lateral striatum from sensory and motor cortices: projections from pericruciate cortex do not extend appreciably into the body of the caudate nucleus, and, as illustrated in Figure 6-14, connections from early visual and auditory cortices are apparently restricted to caudal striatum. Labelling in the contralateral striatum was observed in most experiments, although it was most pronounced in the frontal cortex cases. Contralateral labelling, whenever present, was invariably reduced in volume in comparison to the

ipsilateral side, but was otherwise similar in its spatial and compartmental organization. Unfortunately, for the cortex of the medial hemisphere, we could not establish the existence of contralateral connections even though contralateral labelling was always present. This is because the deposited label infiltrated, to one degree or another, the homotypical cortex that abutted the injected cortex across the median plane.

We will describe thalamic, amygdalar and trans-cortical labelling that we observed in these cases only in so far as it informs the analysis of the site of cortex injected or provides information important for analysis of our findings. Most of the novel and the anticipated connections noted in our material will not be mentioned.

PART I

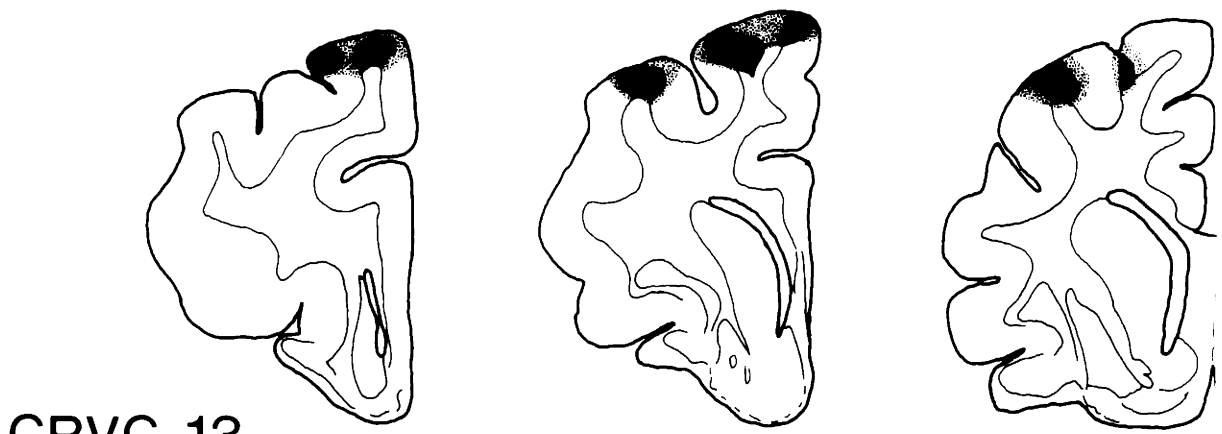
Parietal Cortex

Large deposits of anterograde tracers were made in the posterior parietal cortex of two cats(Fig. 6-1). In case CRCx-8, the crown of the middle suprasylvian gyrus ('area 7'- Hassler and Muhs-Clements, 1964) was blanketed with tritiated amino acids. The resulting injection site, though massive, did not extend appreciably into the lateral bank of the lateral sulcus and so did not involve medial area 7 or visual area 19 (Tusa et al., 1981). There was, however, significant infiltration of the lip and upper part of the lateral bank of the suprasylvian sulcus, including the AMLS and PMLS visual areas of Tusa and colleagues (1981), but probably not the Clare-Bishop area of Sherk (1986). Caudally, the injection site fell short of the border with area 21a. By its positioning and by the cortical and thalamic labelling it elicited, this deposit covered much of area 7p of Olson and Lawler (1987). Inhomogeneous fiber-labelling was observed bilaterally in the caudate nucleus. As we noted in Chapter 4, these posterior parietal fibers appear to take a intermediate position between fibers from the amygdala and from the

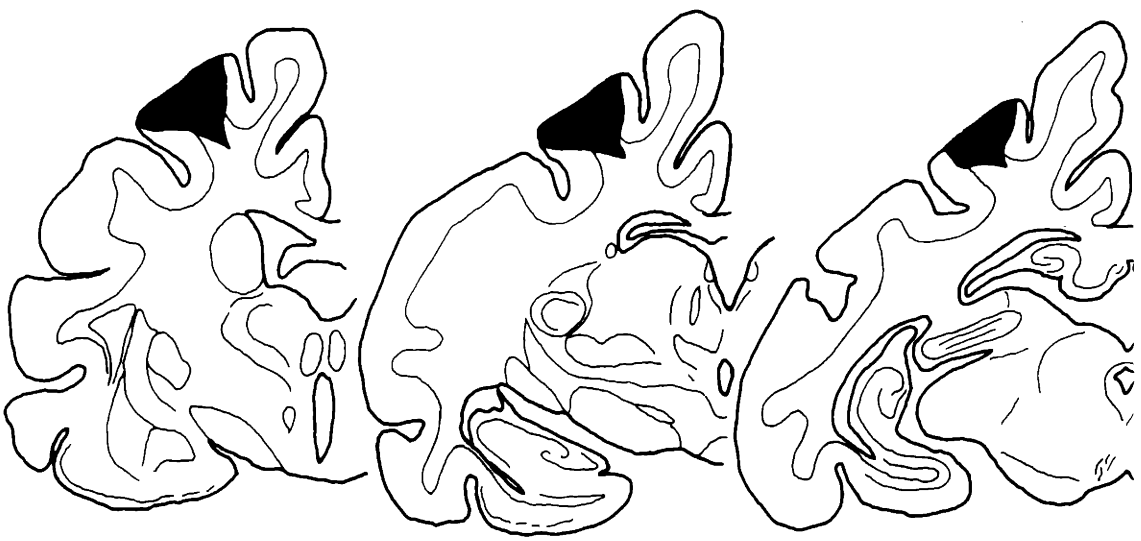
pericruciate cortex (see also Fig. 4-1). In the head of the nucleus, the labelling extended from the dorsomedial corner of the nucleus where the subcallosal fasciculus abuts the lateral ventricle ventrally towards the center of the nucleus. The labelling did not appear to embrace the striatal tissue running along the ventricular face of the nucleus. The labelling was heavier caudally. There, the projection was shifted laterally, away from the ventricle, and, in the suprathalamic body of the caudate nucleus, it took up a dorsolateral position. Labelled fibers were observed, without exception, to avoid the striosomes and innervate matrix tissue (Fig. 6-2A).

The striatal projection of anterior parietal cortex was explored in case CRVC-13 (Fig. 6-1). Radiolabelled amino acids were deposited in the rostral suprasylvian and lateral gyri- mainly within area 5b, but also involving area 5a, including its lateral half where the SIII representation lies (Hassler and Muhs-Clement, 1964; Garraghty et al., 1987). Transcortical labelling included area 4 and, in the thalamus, the oral part of the lateral intermediate nucleus as well as the ventroanterior and ventrolateral nuclei and, to a degree, the medial division of the posterior nucleus, were labelled (Graybiel and Berson, 1980). The ventrobasal complex was unlabelled. These connections are consistent with published reports on the connections of area 5 (Babb et al., 1984; Avendano et al., 1985). Labelled fibers were traced to the dorsolateral caudate nucleus, both encompassing and, apparently, extending somewhat medial to its sensory motor-recipient district. Caudally, the labelling did not reach through the body of the caudate nucleus but petered out at approximately the same transverse level at which the sensory motor-recipient district is eclipsed. Contralateral striatal labelling was not observed in this case. Interestingly, there was virtually no labelling of the putamen and the most lateral part of the dorsolateral caudate nucleus, where fibers from somatic sensory

Figure 6-1: Chartings of injection sites situated in anterior (case CRVC-13) and posterior (case CRCx-8) parietal cortex.

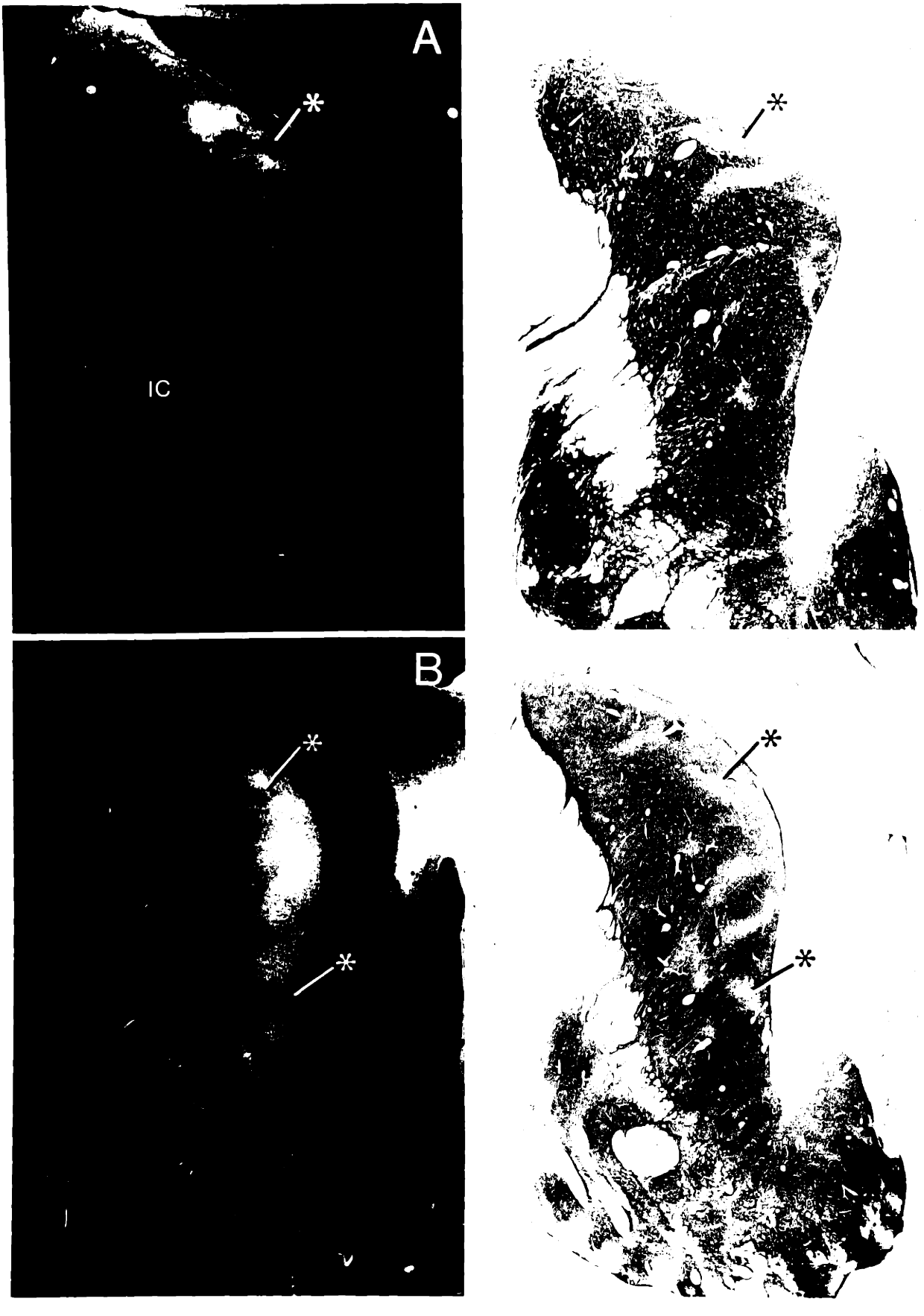


CRVC-13



CRCx-8

Figure 6-2: Corticostriatal fibers from parietal (A) and cingulate (B) cortex preferentially innervate matrix tissue. Autoradiograms (left) illustrate pattern of labelling following deposits of tritiated amino acids in posterior parietal cortex (A: case CRCx-8) and in the 'prelimbic' cortex of the anterior limbic area (B: case CHRC-4r). Asterisks mark correspondences of grain-poor zones with AChE-poor striosomes (right) demonstrated in serially adjoining sections. Abbreviations: IC, Internal capsule.

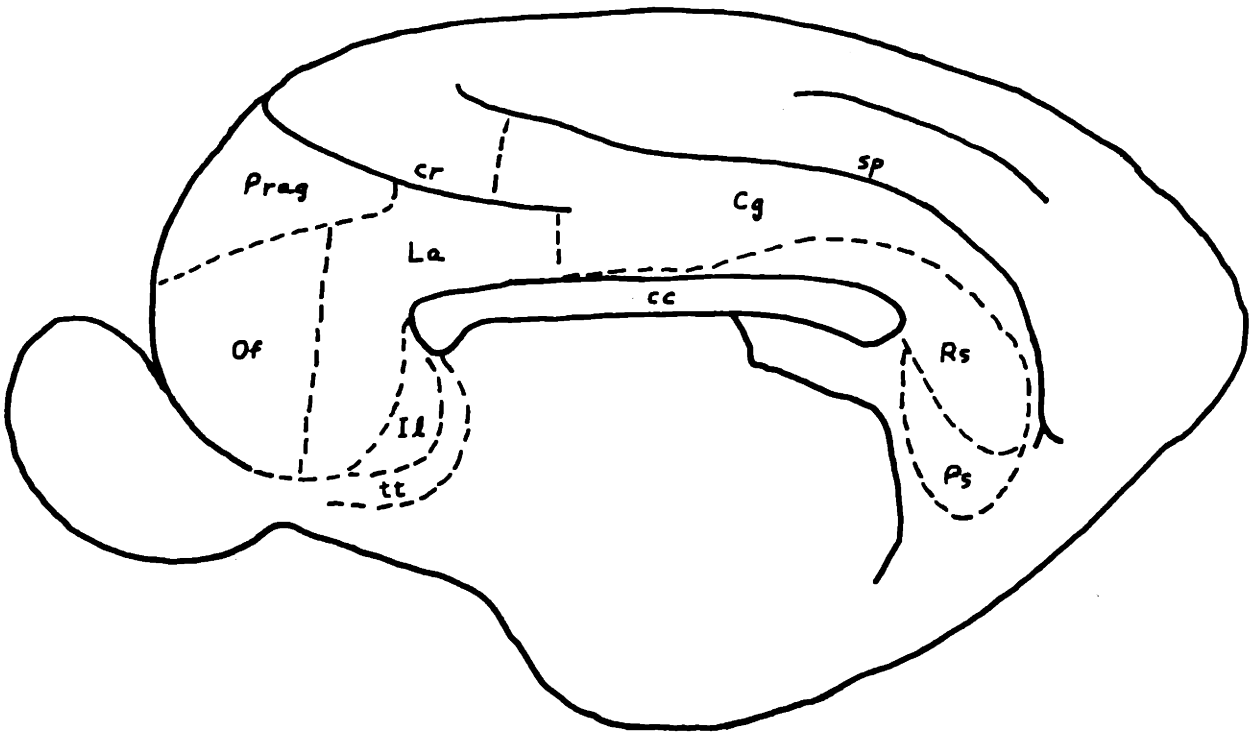

A
*
IC
B
*
*
*
*

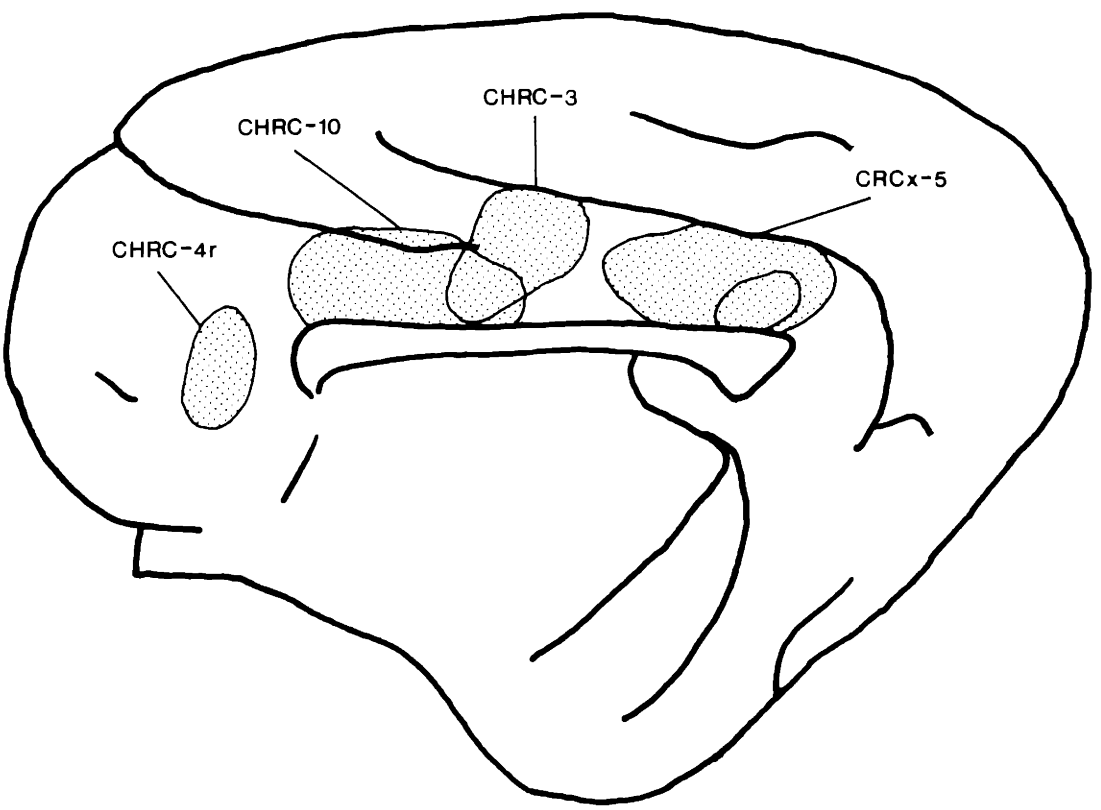
cortex terminate most densely (Malach and Graybiel, 1986), was only lightly labelled. In spite of the difficulties in detecting striosomes in the sensory motor-recipient district of the striatum, we were able, particularly in the rostral half of the nucleus, to relate the fiber-patternings to the AChE-poor striosomes. In every instance, the fibers innervated matrix, and not striosome, tissue.

Cingulate Cortex

The posterior limbic region (Rose and Woolsey, 1948a) was successfully injected with radiolabelled amino acids in six cats (Fig. 6-3. Labelled fibers traced to the striatum terminated in the matrix. The injection site in case CRCx-5 (Fig. 6-3 covered the splenial gyrus adjoining the caudal third of the corpus callosum and extended onto the ventral bank of the splenial sulcus. In anterior thalamus, the anterodorsal nucleus and dorsal and medial parts of the anteroventral nucleus were particularly strongly labelled. Labelling of the anterodorsal nucleus indicates strong involvement of retrosplenial cortex (Niimi et al., 1978; Kaitz and Robertson, 1981). Labelled fibers in the caudate nucleus took up a dorsomedial position close to the ventricle, not reaching as far dorsally as the subcallosal fasciculus but extending ventrally to the genu of the nucleus. In case CHRC-3 labelled striatal fibers were mainly lateral to those of case CRCx-5 (see Fig. 6-16/2). They accumulated in the dorsomedial caudate nucleus along the dorsal quarter of its ventricular face and then cut vertically through the central part of the nucleus, reaching into its ventral half. Labelling extended into the putamen at caudal striatal levels and into the dorsal nucleus accumbens at the rostral pole of the caudate nucleus. The injection site in CHRC-3 (Fig. 6-3 encompassed the rostral end of the cingular area (area 23). Although it appeared to spread into caudal area 24, the absence of labelling in the amygdala suggests that this infiltration was not heavy. In the thalamus, the ventral half of the anteroventral nucleus was strongly labelled and the anterodorsal nucleus was unlabelled.

Figure 6-3: Medial views of the cerebral hemisphere of the cat. Top: Parcellation of medial limbic and medial prefrontal regions of cat cortex, redrawn from Rose and Woolsey (1948a). Bottom: Projection-mapping of selected injection sites situated in medial limbic cortex, all of which elicited labelling of the striatal matrix. Rostral is to the left in this figure. Abbreviations: Cg, Cingular area; cc, Corpus callosum; cr, Cruciate sulcus; Il, Infralimbic area: La, Anterior limbic area; Ps, Postsubiculum; Rs, Retrosplenial area; Of, Orbitofrontal region; Prag, Precentral agranular area; sp, Splenial sulcus; tt, Taenia tecta.


Prag
cr
sp
Cg
La
cc
Of
Rs
Il
Ps
tt


CHRC-3
CHRC-10
CRCx-5
CHRC-4r

Posterior limbic cortex caudal and ventral to the splenium, including the bulk of the ventral retrosplenial area and the cortex of the anterior bank and adjoining lip of the descending limb of the splenial sulcus (Rose and Woolsey, 1948a; Royce, 1982), were not explored in these experiments.

Deposits of radiolabelled amino acids were centered in the anterior limbic area of Rose and Woolsey (1948a) in two cases. In case CHRC-10 we blanketed the part of the anterior limbic area situated dorsal to the corpus callosum (that is, area 24) with a mixture of tritiated proline and leucine (Fig. 6-3). The resulting injection site was massive; it spread laterally into the cruciate sulcus, dorsally to the cortex lying between the cruciate and splenial sulci, and involved areas 23 caudally and 6 rostrally. Thalamic labelling in this case included the anteromedial nucleus, which was very heavily labelled, the anteroventral nucleus, particularly its ventral half, and the dorsolateral-most part of the mediodorsal nucleus. This labelling of the mediodorsal nucleus is consistent with an expansion of the injection site beyond area 24 (Kaitz and Robertson, 1981; Room et al., 1985; Musil and Olson, 1986). In the amygdala the basolateral nucleus and part of the lateral central nucleus were labelled.

Labelled fibers present in the dorsal half of the caudate nucleus collected along the ventricle. Near the genu of the nucleus, the labelling became heavy and traveled as a band centrally through the ventral half of the caudate nucleus and into the dorsal division of the nucleus accumbens. Striatal tissue along the ventricle was unlabelled ventral to the genu. The caudal putamen was broadly labelled. Overall, the labelling in this case was somewhat medial to that seen in case CHRC-3. Study of the compartmental organization of the labelled fibers was compromised by a dump of label in the ipsilateral striatum and by an inferior differentiation of the AChE staining in the dorsal caudate nucleus. We were able to

compare the arrangement of labelled fibers to that of the striosomes in the contralateral striatum and in all instances the fibers avoided the AChE-poor zones. Because of the technical difficulties in this case, however, this finding must be considered provisional in nature.

In case CHRC-4r (Fig. 6-3), a deposit of ^{35}S-methionine was placed rostral to the genu of the corpus callosum within the anterior limbic area. By its position and its labelling of both the anteromedial and mediodorsal nuclei of the thalamus, this injection site lies in the prelimbic cortex (area 32) of the cat as defined by Room et al. (1985). Amygdalar labelling in this case was similar to that seen in case CHRC-10. In the caudate nucleus, labelled fibers accumulated along the ventral three-quarters of the length of the ventricle (Fig. 6-2B). In the ventral half of the caudate nucleus, the label expanded laterally and covered the medial half of the nucleus. There was labelling of all but the medial part of the nucleus accumbens. Thus, the field of striatal labelling in this case largely conformed to the amygdala-recipient striatum as described in Figure 4-1. However, unlike the basolateral amygdalar projection to the striatum, which selectively innervates striosomes (see chapter 4), the projection labelled in case CHRC-4 was to matrix tissue (Fig. 6-2B).

Comment. There were clear topographies in the striatal projections of parietal and cingulate cortex and these topographies fit with the trans-cortical and subcortical connections of the cortices injected. For example, for both the supracallosal posterior cingulate region and the parietal cortex, more rostral cortical projections resulted in more lateral striatal labelling (cf. trans-cortical topographies for these areas in Olson and Lawler, 1987). And, at least for the parietal cortex, the shift in striatal labelling, from dorsomedial to dorsolateral (sensory motor-recipient) caudate nucleus, observed a switch from parietal cortex with connections to visual system to parietal cortex with links to the sensory-motor system.

The total striatal projection from either medial limbic cortex or parietal cortex did not appear to cover the whole of the striatum: no projections to the ventral half of the caudate nucleus were detected in any parietal cortex case and cingulate cortex did not appear to project into dorsolateral caudate nucleus (but see the retrograde labelling data of Kubozono et al., 1986). Taken together, though, parietal and medial limbic cortex provide input to most, if not all, of the striatal matrix.

The striatal projections of the parietal and limbic cortices appeared to overlap, at least in part. This was tested directly in case CHRC-13, in which the posterior parietal cortex was blanketed with an HRP-WGA conjugate and a large deposit of ^{35}S-methionine was placed in the splenial gyrus and adjoining ventral bank of the splenial sulcus, at mid-rostrocaudal levels of the cingular area. Comparisons of serially adjoining sections through the striatum established definite overlap, and not interdigitation, of these two projections. The bulk of both connections, however, were spatially separate, with the cingulate terminal field lying medial and somewhat ventral to the parietal field. Consultation of our cases suggests that the overlap would have been more extensive if we had placed our cingulate deposit more rostrally, near the area 23/area 24 border, as in case CHRC-3 (see Fig. 6-16/1,2). Somewhat similar conclusions concerning overlap between cingulate and parietal projections, based wholly on cross-case comparisons, have been made by Yeterian and Van Hoesen (1978) in the monkey.

These projections to matrix tissue did not show the strongly heterogeneous labelling-pattern sometimes seen after restricted cortical injections (see Part III and Malach and Graybiel, 1986). Neither, however, did they always present an even and diffuse field of matrix labelling disrupted only by fiber-poor zones that corresponded to striosomes. Rather, the projections often had a sculpted

appearance, as if forming figures, albeit large ones, within matrix tissue. This arrangement was most prominently seen in contralateral (and therefore reduced in volume) projections, such as that labelled from posterior parietal cortex in case CRCx-8. The implications of such a modest form of matrix inhomogeneity are obscure.

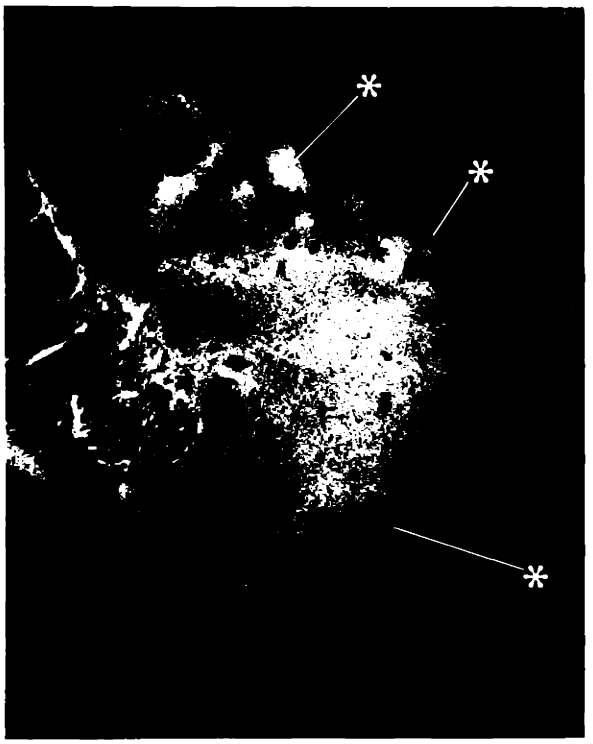
PART II

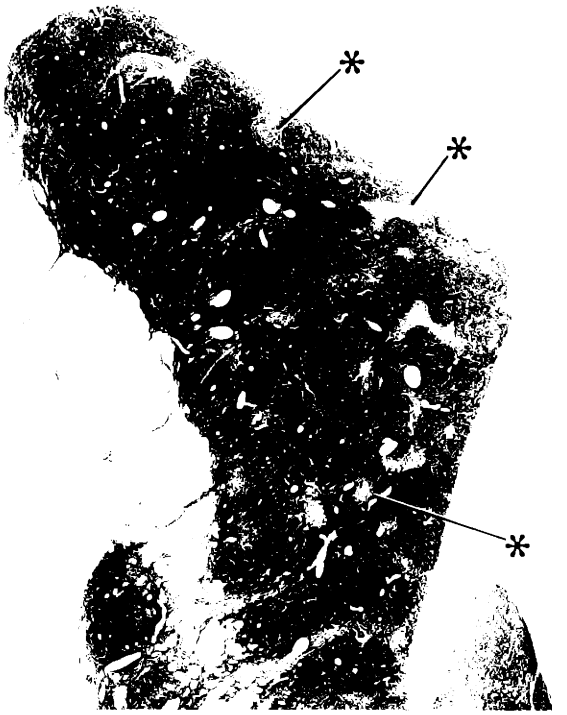
Prefrontal Cortex

In our initial examination of the compartmental organization of corticostriatal connections, we reported three cases in which massive deposits of radiolabelled amino acids were centered in that part of area 6 that lies on the medial anterior sigmoid gyrus. Figure 6-4 illustrates the pattern of striatal terminations observed in these experiments. There was massive, inhomogeneous fiber-labelling through much of the caudate nucleus. In the dorsal half of the nucleus, there were circumscribed patches of labelled fibers and these filled the striosomes precisely. In the ventral half of the nucleus, the fiber-labelling was broader and more even. It was broken up, though, not by patches but by vacancies in the labelling. These vacancies corresponded to the AChE-poor striosomes. Because the deposits in these first cases were massive and shared the same location, it seemed possible that the observed 'dorsal fill-ventral avoid' pattern was due to involvement of at least two cortical areas, one that projected dorsally in the caudate nucleus and innervated striosomes and another that reaches the matrix tissue ventrally. To explore this possibility, we placed sixteen deposits of varying size throughout the prefrontal cortex and examined the compartmental distribution of the labelled projections.

In two cases, we made massive deposits of tritiated proline into the gyrus proreus. The resulting injection sites covered the gyrus but did not substantially

Figure 6-4: Photomicrographs of serially adjoining sections through the caudate nucleus illustrate the dorsal 'fill'/ventral 'avoid' pattern of affiliation with striosomes seen following large deposits of anterograde tracers into the frontal cortex. Asterisks on right mark AChE-poor striosomes that are enriched (dorsal) or impoverished (ventral) in labelled fibers in the autoradiogram depicted on the left. Taken from case CRSSC-9r, in which a massive deposit of ^{35}S-methionine was centered in area 6 of the contralateral hemisphere.



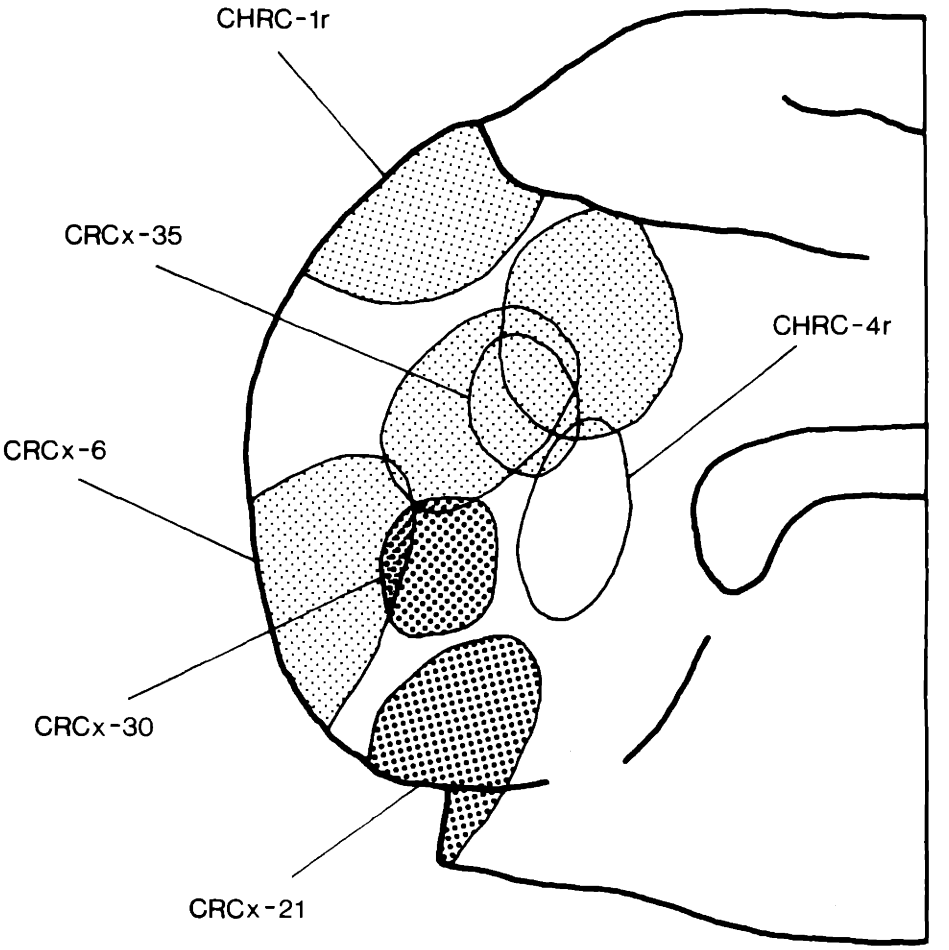


infiltrate caudally adjoining area 6aβ of the medial anterior sigmoid gyrus (areal designation from Hassler and Muhs-Clements, 1964). Labelling in the striatum was again massive and inhomogeneously distributed and was arranged in a pattern of dorsal fills and ventral avoids of striosomes. The field of striatal labelling differed, though, from that of the area 6 cases. Fiber-labelling in the proreal cases did not reach into the dorsolateral (sensory motor-recipient) caudate nucleus and, instead, extended to the base of the nucleus.

We also made tracer-deposits of small to moderate size in prefrontal cortex. Figure 6-5 illustrates injection sites for a selection of these cases. Although the sites shaded in light stipple are largely non-overlapping, they all elicited a pattern of dorsal fills and ventral avoids in their projections to the striatum. The striatal fields of termination, though, shifted with injection site position. For example, in case CHRC-1r, the labelling was principally in dorsal and central caudate nucleus, whereas in case CRCx-6 the labelling was situated medially and ventrally.

Four common features of the double innervation-pattern seen in these prefrontal cases were of special note. First, it was frequently difficult to detect inhomogeneities, and to score them with respect to striosomes, in the zone of transition between the 'fill' and 'avoid' patterns. This was particularly true for the fiber-labelling on the ipsilateral side after large cortical deposits. Second, the transition between dorsal fills and ventral avoids was, more properly, a transition between dorsal and somewhat lateral fills and ventral and somewhat medial avoids. In other words, the elevation of the transition was not in the horizontal plane, but ran at a modest angle to it, from dorsomedial to ventrolateral. Third, the dorsal fill-ventral avoid pattern could be followed caudally at least to the level of the rostral body of the caudate nucleus in every case in which the histochemistry permitted compartmental evaluation of the fiber-distributions. Fourth, near the

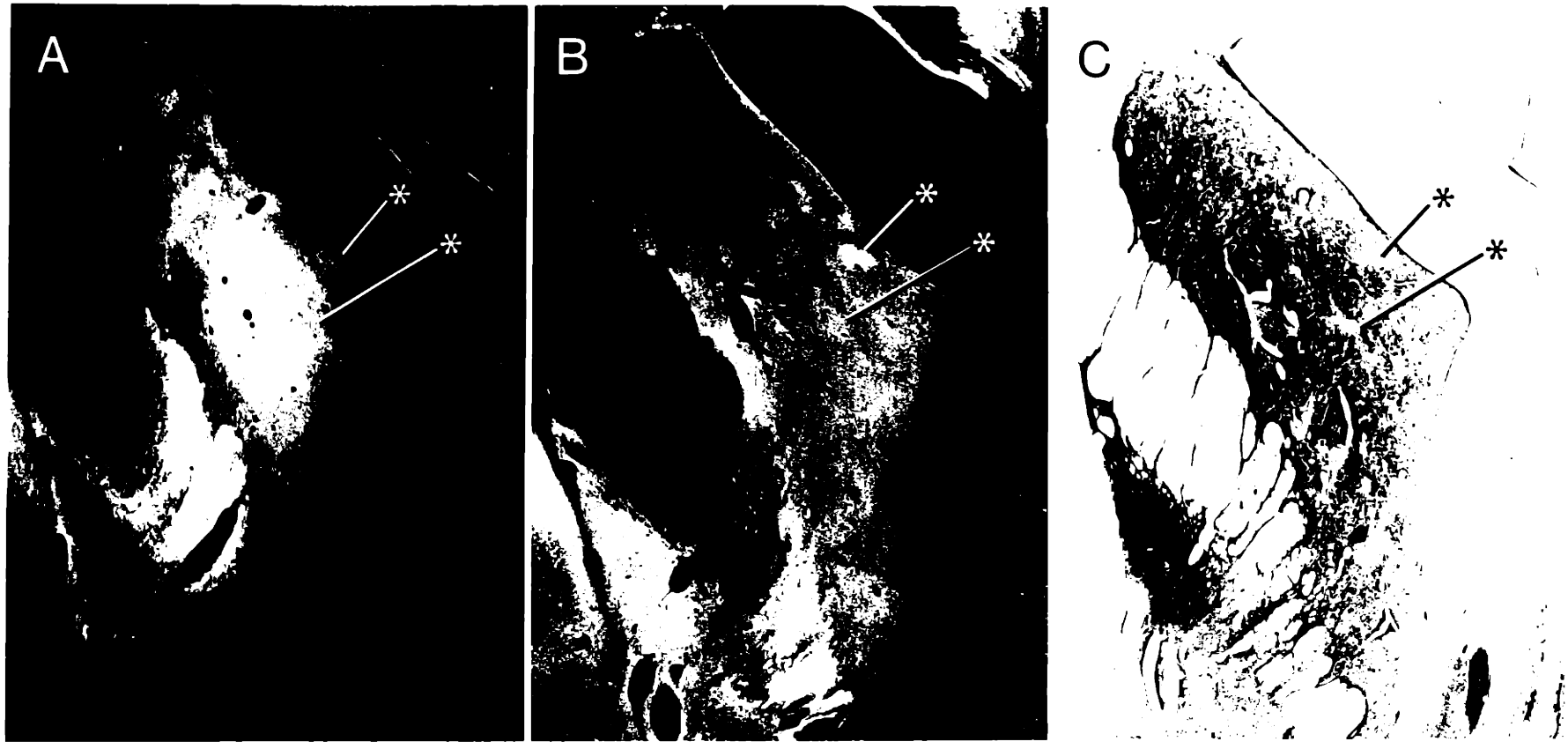
Figure 6-5: Medial view of rostral end of cat's hemisphere illustrating a selection of the injection sites that were situated in medial prefrontal cortex. Sites marked by light stipple elicited a "dorsal fill-ventral avoid" pattern of compartmental labelling in the striatum; sites highlighted by heavy stipple produced predominately striosomal labelling in ventral caudate nucleus. The relative position of case CHRC-4r of the medial limbic series, which showed labelling of the striatal matrix, is presented for purposes of comparison. The injection sites of several of these cases, such as CHRC-1r and CRCx-6, extended to cortex of the lateral hemisphere (not illustrated).


CHRC-1r
CRCx-35
CHRC-4r
CRCx-6
CRCx-30
CRCx-21

rostral pole of the caudate nucleus, labelled fibers innervated striosomes throughout most of the cross-sectional area of the nucleus. Avoids, when detected, were situated more ventrally than at more posterior longitudes.

Case CHRC-1. Although, as we noted, deposits in different parts of prefrontal cortex produced labelling in different striatal districts, there was still generous opportunity for overlap in the striatum among the projections from different parts of frontal cortex. The question arose whether the position of zone of transition between the fill and avoid patterns, which was present in each of these cases, was identical across the experiments, or whether it moved. Our impression from the separate cases was that the elevation at which the pattern changed from fills to avoids shifted with movements of the terminal field. We tested this impression directly in case CHRC-1. A large deposit of a cocktail of tritiated proline, leucine and lysine was set in area 6 at the junction of the medial anterior sigmoid gyrus and the medial hemisphere (CHRC-1r in Fig. 6-5). A second deposit, of HRP-WGA, was placed in the lateral face of the gyrus proreus of the same hemisphere. In addition, a rostroventral part of the anterior sigmoid gyrus and adjoining lateral bank of the praesylvian sulcus received an injection of the lectin-peroxidase conjugate. Figure 6-6depicts a run of three sections through the caudate nucleus of cat CHRC-1, prepared for autoradiography (A), and peroxidase (B) and AChE (C) histochemistry. The labelled projections overlapped extensively in the striatum and comparisons with the AChE staining established that both projections both filled striosomes dorsally and avoided them ventrally. Close examination, though, indicated that there is a short stretch of central caudate nucleus where the fibers labelled radiographically began to avoid striosomes while the fibers labelled enzymatically continued to innervate them. In other words, the transition in compartmental innervation does change its elevation according to cortical region

Figure 6-6: Shifting pattern of compartmental affiliation documented for case CHRC-1, in which radioactive tracer was placed in dorsomedial prefrontal cortex and HRP-WGA was delivered to ventrolateral prefrontal cortex. Illustrated are three serially adjoining sections prepared for autoradiography (A) and peroxidase histochemistry (B), and stained for AChE activity (C). Upper asterisks mark AChE-poor striosome filled by both labelled projections; lower asterisks indicate striosome filled by the enzymatically labelled fibers (B), and avoided by the radiolabelled fibers (A). Short broad arrows in ventral caudate nucleus note AChE-poor striosomes avoided by both projections.

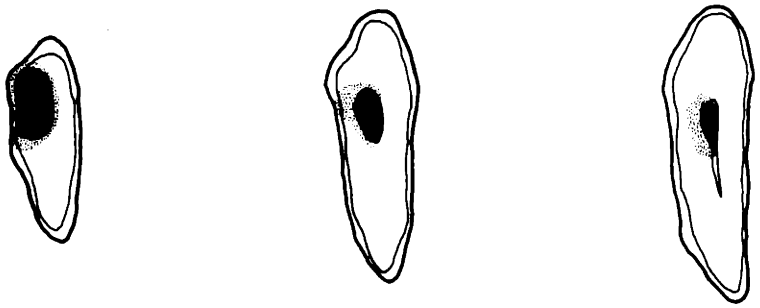

A
B
C

injected. In this example, the transition for the projection from dorsomedial frontal cortex occurred *dorsal* to that for ventrolateral frontal cortex. As we will demonstrate in the discussion, this finding of a shifting border for the dorsal fill-ventral avoid transition, while not guaranteeing that single areas of cortex participate in this dual pattern of innervation, does pose topological difficulties for any scheme in which areas of prefrontal cortex are restricted to single projection-patterns.

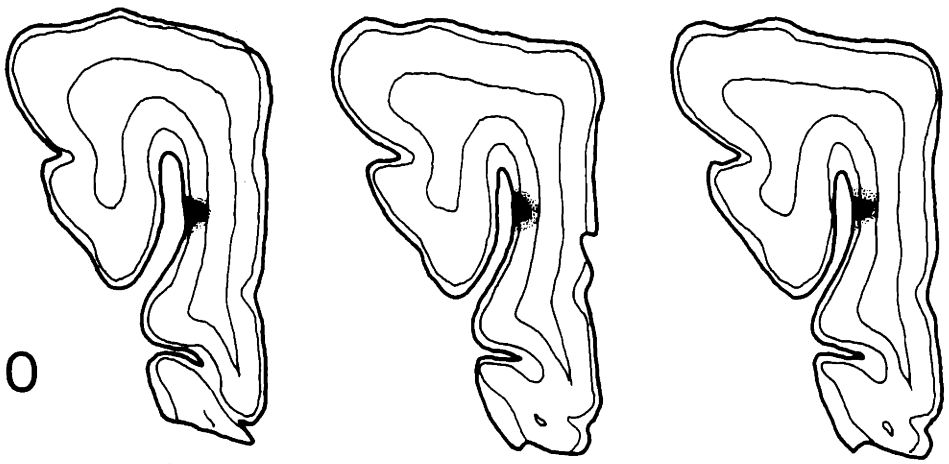
Small deposits in prefrontal cortex. A conclusion that cortical areas have dual patterns of compartmental innervation predicts that these patterns can be elicited with very restricted injection sites. We therefore attempted to make very small deposits of anterograde tracer into prefrontal cortex. We were successful in three cases. In case CHRC-9r (Figs. 6-5 and 6-7), the deposit was positioned near the rostral pole of the gyrus proreus, somewhat dorsally and extending slightly onto its lateral surface. The injection in case CRCx-25 (Fig. 6-7) was placed in the deep layers of medial prefrontal cortex, near the ventral border of area 6m of Olson and Jeffers (1987). The deposit in case CRCx-10 (Fig. 6-7) was buried in the praesylvian sulcus, in the center of its medial bank. Because of the small size of the deposits in these cases, we were able to elicit striatal labelling of sufficient density to permit comparisons with the histochemical compartments only by exposing the autoradiograms for long periods of time (CHRC-9r, 54 weeks; CRCx-10, 22 months; CRCx-25, 33 weeks; the chartings for the injection sites for cases CHRC-9r and CRCx-25 were drawn from material with these exposure times). In spite of the small size and wide separation of these deposits, a pattern of dorsal fills and ventral avoids was observed in each of these cases (see charting of sections from case CHRC-9 in Fig. 6-16/4). Interestingly, in cases CRCx-25 and CRCx-10, the dorsal fills were more readily identified in sections from the rostral caudate nucleus.

Figure 6-7: Chartings of injections sites in three cases in which very small deposits consisting of equal parts ^{3}H-proline and ^{3}H-leucine were placed in prefrontal cortex. The sections illustrated are closely spaced and cover the rostro-caudal extents of the injection sites' cores. Exposure times for the autoradiograms studied in preparing this figure: CHRC-9, 54 weeks; CRCx-10, 4 weeks; CRCx-25, 33 weeks.

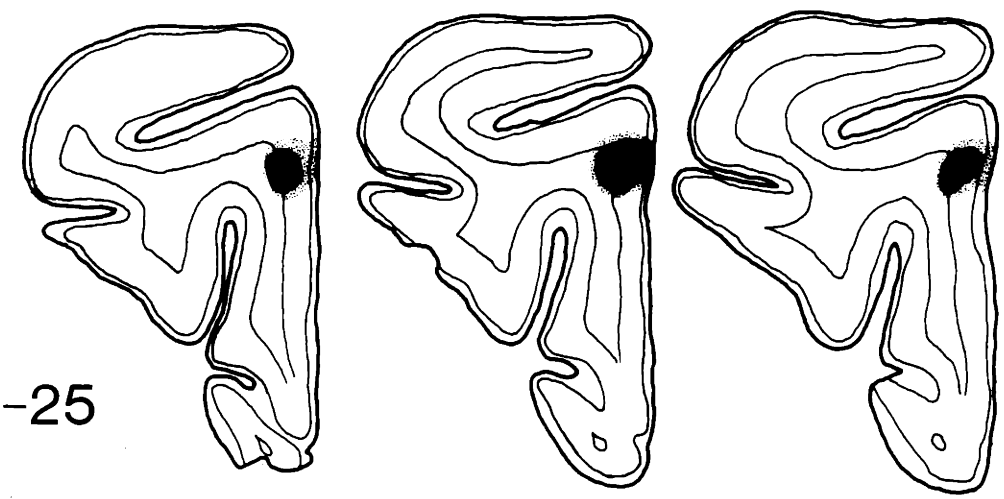
CHRC-9r



CRCx-10



CRCx-25



Caudal ventromedial prefrontal cortex. Three prefrontal cases did not present a dorsal fill-ventral avoid pattern of striatal labelling. The deposits of label in these cases were placed in the ventromedial prefrontal cortex, rostral to the anterior limbic area of Rose and Woolsey (1948a) and caudal to the rostroventral quadrant of the medial prefrontal cortex that was injected in case CRCx-6 (Fig. 6-5. Labelled fibers were distributed to the nucleus accumbens and to the medial and ventral caudate nucleus, where they were densely concentrated in the striosomes. There was also moderate labelling of the matrix tissue which was most pronounced ventrally and medially within the termination-field. In cases CRCx-21 and CRCx-43 (deposit not shown), heavily labelled striosomes were identified as far ventrally as the border between the nucleus accumbens and the caudate nucleus (stipulated as the plane running from the fundus of the lateral ventricle to the anterior radiations of the anterior commissure), and in case CRCx-21 labelled fibers collected within SP-rich zones of the dorsal division of nucleus accumbens that may be homologous to the striosomes of the dorsal striatum (see chapter 4). Case CRCx-30, the injection site of which was centered somewhat dorsal and anterior to those of the other two cases, showed a different pattern of labelling in that we could not confirm selective fills of striosomes in the ventromedial-most corner of the caudate nucleus. Labelled fibers there appeared to innervate both compartments equally.

Comment. The striatal projection of prefrontal cortex is topographically organized: ventromedial deposits elicited labelling that was more medially situated than that seen after more lateral (e.g., lateral gyrus proreus) or dorsal (e.g., area 6) injections; and more dorsal striatal labelling was produced by the more dorsally situated prefrontal deposits. Prefrontal terminal-fields in the striatum were considerably more extensive in the dorsoventral axis than in the mediolateral one.

This arrangement apparently permitted a second level of organization along this dimension: All deposits in prefrontal cortex led to labelling of striosomes in the caudate nucleus. However, most prefrontal cases showed a dual pattern of innervation whereby labelled fibers preferentially innervated striosomes dorsally and matrix tissue ventrally within their field of termination. The striatal elevation at which this switch in compartmental affiliation occurred moved with injection site location. Roughly put, the topography of this shift was that more ventral prefrontal deposits led to a more ventral striatal position for the transition. Thus, this is a secondary topographic mapping superimposed on a primary mapping that established the total field of striatal innervation. The three cases with deposits in the caudoventral quadrant of medial prefrontal cortex apparently represent the ventral limit of the dorsal fill-ventral avoid topography: there were no examples of labelled fibers selectively innervating matrix tissue. In theses cases, striosomes were heavily labelled to, or nearly to, the ventral boundary of the dorsal striatum.

The amygdalar and thalamic labelling observed in the prefrontal experiments also shifted with injection site position. All cases showed labelling of the ventromedial and rostral and paralaminar ventroanterior nuclei and of the mediodorsal nucleus. The locus of mediodorsal nucleus labelling moved medially, from the lateral half of the nucleus to its central core (and labelling in the paratenial nucleus became, first, apparent and then pronounced) with more ventral placements of the site of injection. Anterograde labelling of the lateral half of the basolateral nucleus was detected in nearly every prefrontal case, but the volume of the connection was substantial only in cases with ventral injection sites. The ventromedial prefrontal experiments, including both cases such as CRCx-21 with caudal deposits and those such as CRCx-6 with rostral deposits, elicited the heaviest amygdalar innervation. In this material, the full basolateral nucleus was

labelled (most densely at caudal levels), as were the dorsolateral part of rostral basomedial nucleus and a medial part of the lateral central nucleus.

The cases with the most ventral 'fills' of striosomes, that is, CRCx-21 and CRCx-43, and *not* the slightly more dorsal CRCx-30, were distinguished from all other cases by the extreme medial placement of the labelling in thalamus. This included labelling at the medial limits of the ventroanterior and ventromedial nuclei and in a dorsomedial part of the rostral mediodorsal nucleus that was labelled in no other case.

Motor Cortex

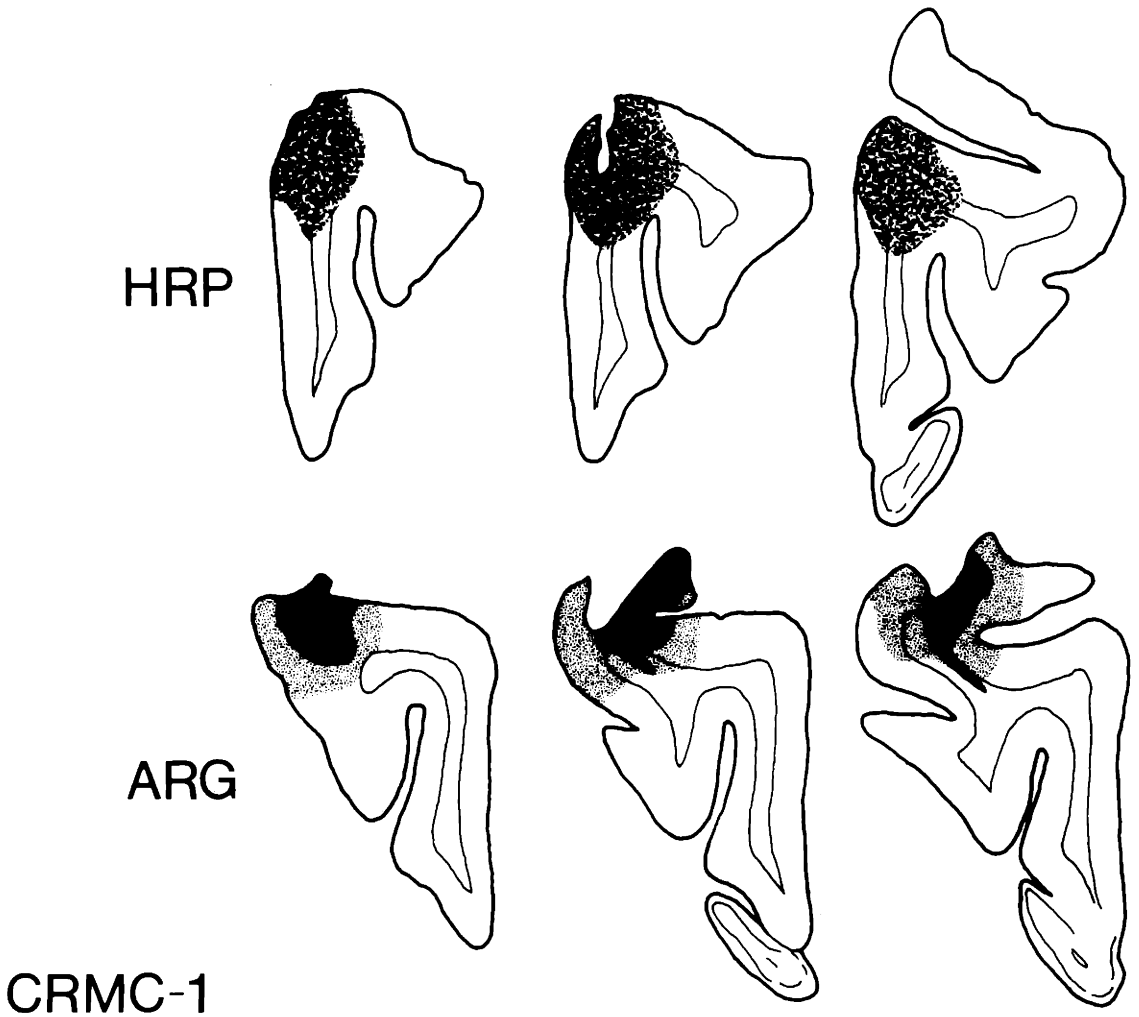
Situated dorsally in frontal cortex, at the opposite extreme from the ventromedial prefrontal cortex that selectively innervates striosomes, is primary motor cortex- area 4γ of the cat (Hassler and Muhs-Clement, 1964; Nieoullon and Rispal-Padel, 1976). Striatal projections from this pericruciate region were studied in five cats. In every case labelled fibers were inhomogeneously and bilaterally distributed in the dorsolateral striatum (the dorsolateral head of the caudate nucleus and the dorsal half of the rostral putamen; see Fig. 4-1). It is often difficult in this striatal sector to detect striosomes by AChE staining (Graybiel and Ragsdale, 1978b). In fact, comparison was not possible in one case; and in the four other cases we were able to score the labelled fibers with respect to the AChE staining only for a part of the terminal field, usually its ventral half. In nearly every example, the labelled fibers avoided the enzyme-poor zones.

To overcome this technical difficulty, we attempted to label dorsolateral striosomes in our motor cortex cases in two additional ways: histochemistry for SP-like immunoreactivity and experimental labelling of fibers from area 6aβ of the medial anterior sigmoid gyrus and the rostral fundus of the praesylvian sulcus. Both of these methods have been shown to label AChE-poor striosomes in

experiments in which the AChE staining of dorsolateral caudate nucleus was well-differentiated (Graybiel et al., 1981; Graybiel and Chesselet, 1984; Bolam et al., 1987; Ragsdale and Graybiel, 1981). Figure 6-9 illustrates our findings for case CRMC-1, one of two double-labelling experiments. In the left hemisphere, ^{35}S-methionine was delivered to area 4γ; HRP-WGA was deposited in area 6aβ of the right hemisphere (Fig. 6-8). The striatal projection labelled by the peroxidase-lectin conjugate extended into the sensory motor-recipient sector at rostral levels in this case. Comparison of the labelling-patterns elicited by the two tracers established that the projections interdigitate (Fig. 6-9B,C), which implies that the area 4 projection is directed principally to matrix tissue. At levels chosen for illustration, inhomogeneities were also seen in the AChE stained tissue (Fig. 6-9A). Bilateral comparisons confirm area 4γ distributions to the matrix compartment and area 6aγ distributions to the striosome compartment dorsally. It is crucial to note, though, that area 4γ was *not* as heavily labelled in case CRMC-1 as in other pericruciate cases, and that the resulting striatal labelling did not extend as far medially (compare, for example, Fig. 6-9B with Fig. 4-1C).

We were able to relate the striatal distribution of fibers from pericruciate cortex with striosomes identified by SP immunohistochemistry in case CRMC-4. The pericruciate fibers were labelled by deposits of ^{35}S-methionine that blanketed area 4γ (Fig. 6-8). In the striatum, along the dorsolateral cap of the caudate nucleus and dorsocentrally along the medial striatal reach of the pericruciate fibers, the projection terminated within the SP-positive striosomes. This was particularly clear, and quite selective, in the contralateral caudate nucleus. Throughout most of the dorsolateral caudate nucleus, though, the labelled fibers mainly innervated the matrix compartment, although some striosomes were lightly to moderately labelled. Interestingly, this matrix innervation was not homogeneous: there were zones of

Figure 6-8: Chartings of injection sites for two motor cortex cases. In case CRMC-1, HRP-WGA was injected into area 6 of the right hemisphere (HRP) and ^{35}S-methionine was delivered to area 4γ of the left hemisphere (ARG). In case CRMC-4, a large deposit of ^{35}S-methionine was placed in motor cortex.


HRP
ARG
CRMC-1

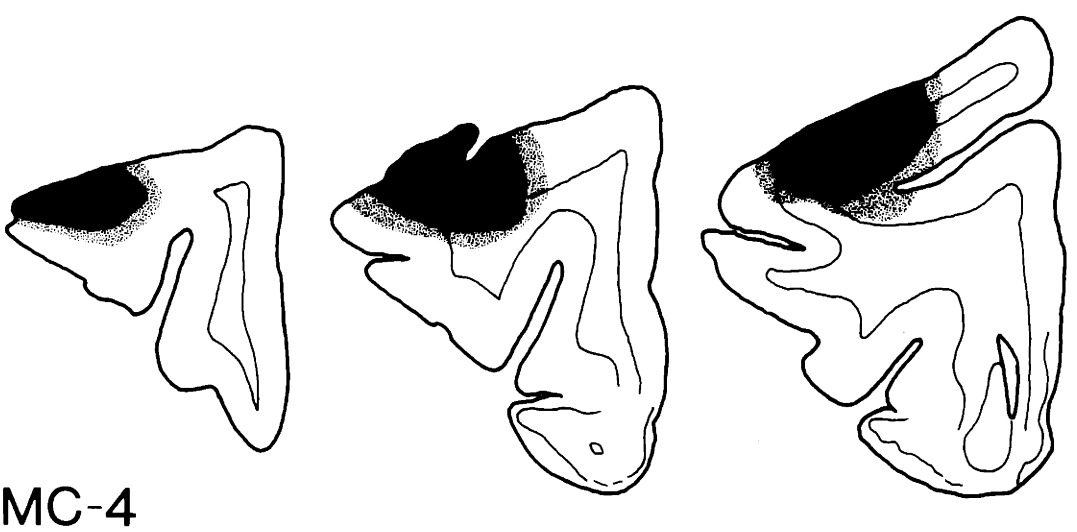

CRMC-4

Figure 6-9: Photomicrographs of three serially adjoining sections taken from case CRMC-1, and prepared for AChE histochemistry (A), autoradiography (B) and HRP histochemistry (C). Asterisks indicate striosomes labelled by AChE staining (A) and by HRP-WGA deposits into area 6 (C) that are avoided by fibers from area 4 (B).


A
AC

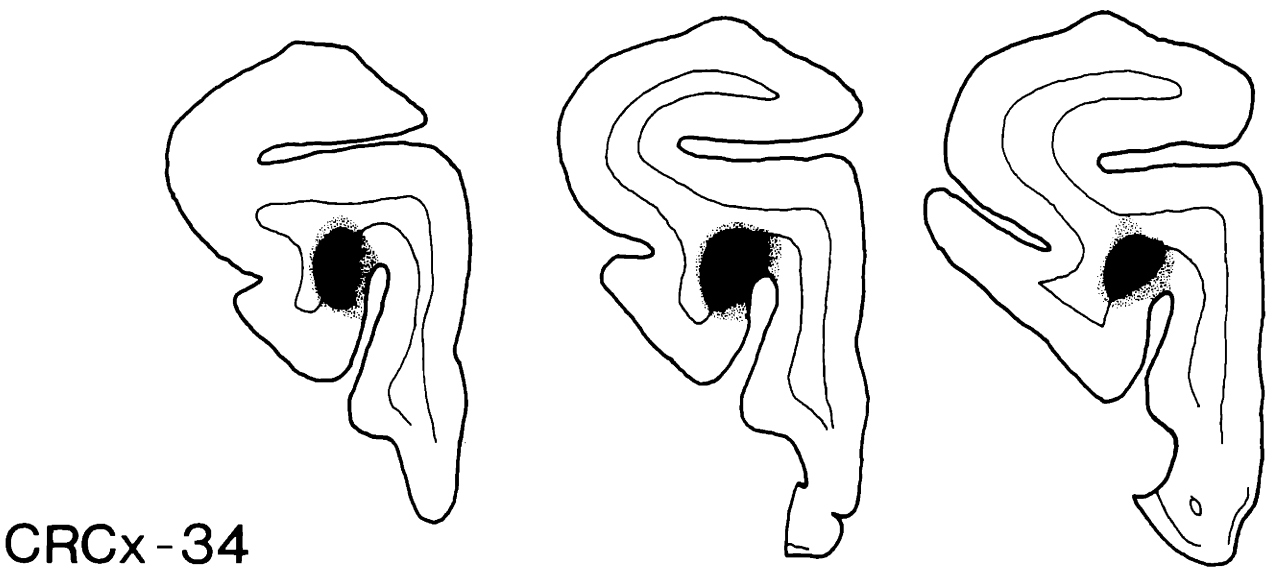
very light labelling whose borders were not predicted by compartmental boundaries. Finally, in the ventral half of the striatal field of labelling, the cortical fibers clearly avoided the striosomes.

Comparison of the striatal distribution of pericruciate fibers with chartings of the projections of somatic sensory areas 3a and SI (Malach and Graybiel, 1986) indicated that the somatic sensory-recipient sector of the striatum is largely contained within the pericruciate cortex-recipient sector (cf. similar conclusions from cross-case comparisons by Kemp and Powell (1970) and Kunzle (1975, 1977). The pericruciate zone, however, appears to be more extensive, especially medially and dorsally within the caudate nucleus. In particular, the striatal zones in which we observed 'fills' of striosomes in case CRMC-4 appear to lie beyond the distribution of fibers from primary somatosensory cortex (although within the projection-field of caudally adjoining area 5 of parietal cortex- see Part I). Because the injection sites in the pericruciate cases, although centered in area 4γ, were quite large, and because establishing the limits of any ^{35}S-methionine deposit is always problematic, we can not conclude that the most medial striatal labelling we observed, including the selective innervation of striosomes, issued from the motor cortex, and not from rostrally adjoining fields.

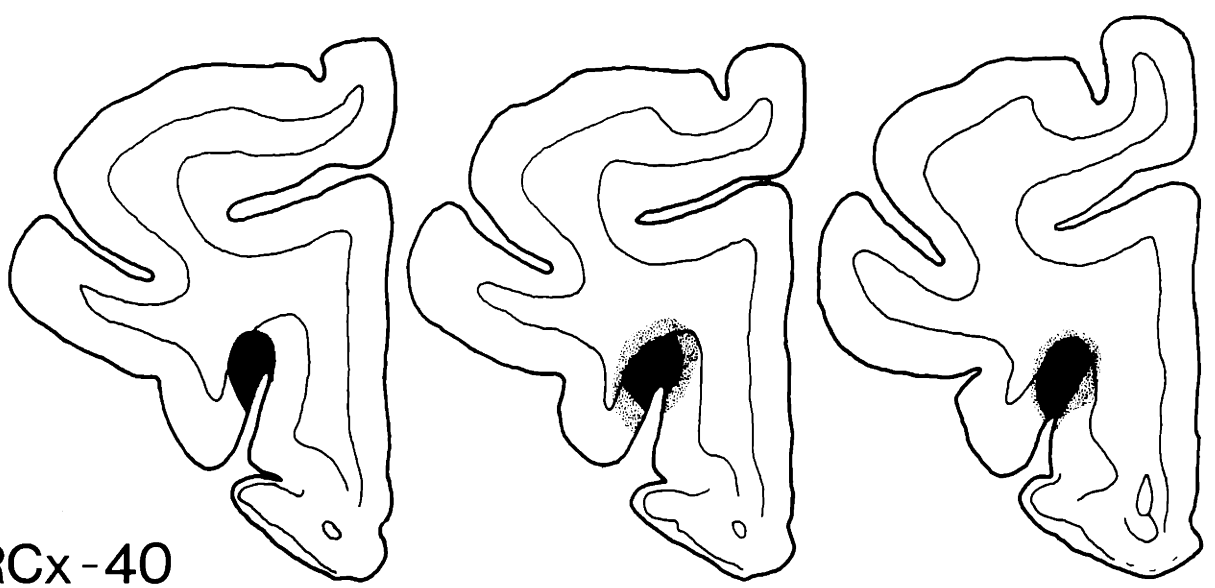
Lateral Praesylvian Cortex

The cortex of the lateral bank of the praesylvian sulcus may provide additional input to striosomes situated in the sensory motor-recipient sector of the striatum. This cortex was successfully injected in two cases, CRCx-34 and CRCx-40 (Fig. 6-10). The injection sites were centered in the upper part of the lateral bank, but involved most of the lateral bank and also the fundus. They were essentially non-overlapping, with case CRCx-34 situated anteriorly in the sulcus. Together, these deposits covered most of the lateral oculomotor area of Guitton

Figure 6-10: Chartings of injection sites placed in lateral praesylvian cortex in cases CRCx-34 and CRCx-40.



CRCx-34



CRCx-40

and Mandl (1978a). The striatal labelling elicited by these deposits was extremely similar. There was fiber-labelling in the lateral half of the striatum which, dorsally, was organized into patches. These patches were present in, but not restricted to, the sensory motor-recipient sector of the caudate nucleus. Ventrally in the caudate nucleus and throughout the rostral putamen, the labelling was denser and more homogeneously distributed. The dorsal patches coincided with zones rich in SP-immunoreactive cells and weak in AChE activity. Grain-poor zones were detected within the broadly distributed terminal-field of the ventrolateral caudate nucleus and these matched the striosomes.

Case CRCx-40 differed from case CRCx-34 in showing some label in the in the ventral part of the basolateral nucleus of the amygdala and significant label in lateral olfactory tubercle. This case also presented labelling of the ventral agranular insula area of Krettek and Price (1977a) and, possibly, of the basal ventromedial nucleus. Some of this additional labelling may have been due to involvement either of the gustatory area situated rostroventrally in the lateral bank of the praesylvian sulcus or, possibly, of the olfactory related lateral orbital cortex of the medial bank (Burton and Earls, 1969; Wiegand and Price, 1982; Yasui et al., 1987). The two cases shared transcortical labelling of area 5 and area SIV and light labelling of the deep layers of area 4. Their principal thalamic labelling was of the lateral ventromedial and medial ventrolateral nuclei in the ventral tier and of the caudal mediodorsal nucleus.

In cat CRCx-19, injection site labelling was somewhat broader than that of cases CRCx-34 and CRCx-40 and included the fundus and both banks of the rostral end of the praesylvian sulcus. Labelled projections in this case were quite similar to those of case CRCx-40.

Insula Cortex

Figure 6-12A illustrates the striatal labelling we saw after deposits into insula cortex. Well-circumscribed patches of labelled fibers were distributed throughout most of the central core of the caudate nucleus. In the ventral third of the nucleus, and particularly at its base, the labelling was not restricted to patches, but had a broader distribution. Figure 6-12B depicts a nearby pair of serially adjoining sections that demonstrates that the patches of label correspond to AChE-poor striosomes. Thus, the insula cortex provides the most widespread innervation of striosomes of any cortex we have examined in the cat. The full network of labelled striosomes was not visible in this example because the autoradiogram was underexposed (four weeks) to permit an analysis of the labelling-pattern at the base of the caudate nucleus. Labelled fibers there innervated matrix tissue heavily and striosomal tissue lightly (Fig. 6-12B).

Figures 6-12A and 6-12B illustrate sections taken from case CRCT-1R, in which the insula was injected anteriorly. We made eight deposits into insula cortex (Fig. 6-11) and, in spite of the differences across the cases in the size and location of the injection sites, in every case we observed broad labelling of striosomes throughout most of the caudate nucleus and strong matrix labelling at the base of the nucleus. In over half of the cases, we were able to confirm that this matrix fiber-labelling selectively avoided striosomes. In every case this pattern of striosome labelling dorsally and matrix labelling ventrally could be followed through the caudal head of the caudate nucleus, and in several of the posterior insula cases this caudal labelling was particularly heavy. In no case did the fiber-labelling extend appreciably into the nucleus accumbens or reach striatal tissue immediately adjoining the ventricle.

Thalamic labelling in these cases was elicited in the ventromedial and

Figure 6-11: Lateral view of left cerebral hemisphere of the cat, illustrating a selection of the injection sites placed in insular and temporal cortex. Sites marked in stipple evoked selective labelling striosomes; sites not shaded elicited complex labelling of the striatal matrix. Sites outlined in broken lines are sensory cortex deposits that elicited labelling in caudal striatum. The approximate transition between rostral and caudal temporal cortex, defined by the compartmental organization of the projection to striatum, is indicated by the injection site borders of cases CRCx-37 and CRCx-44R.

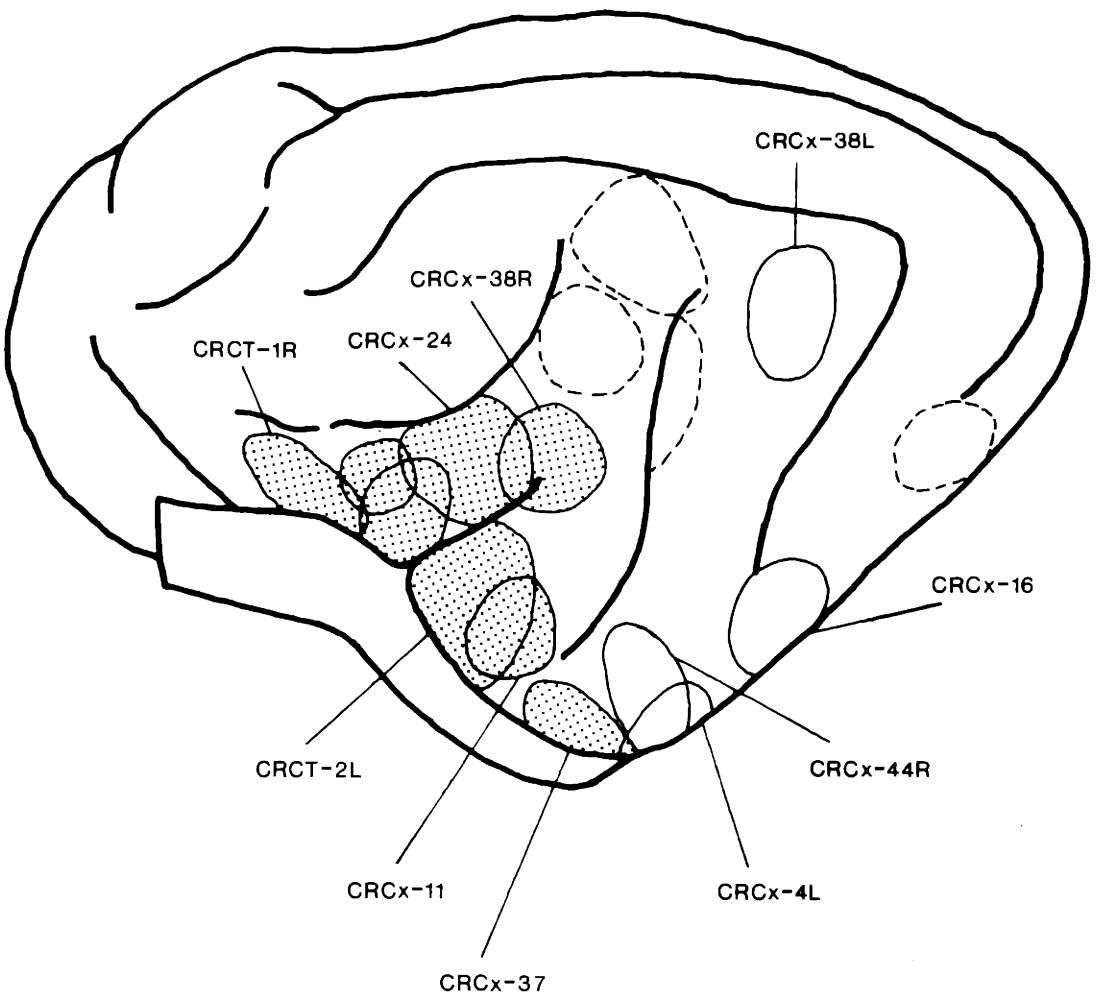
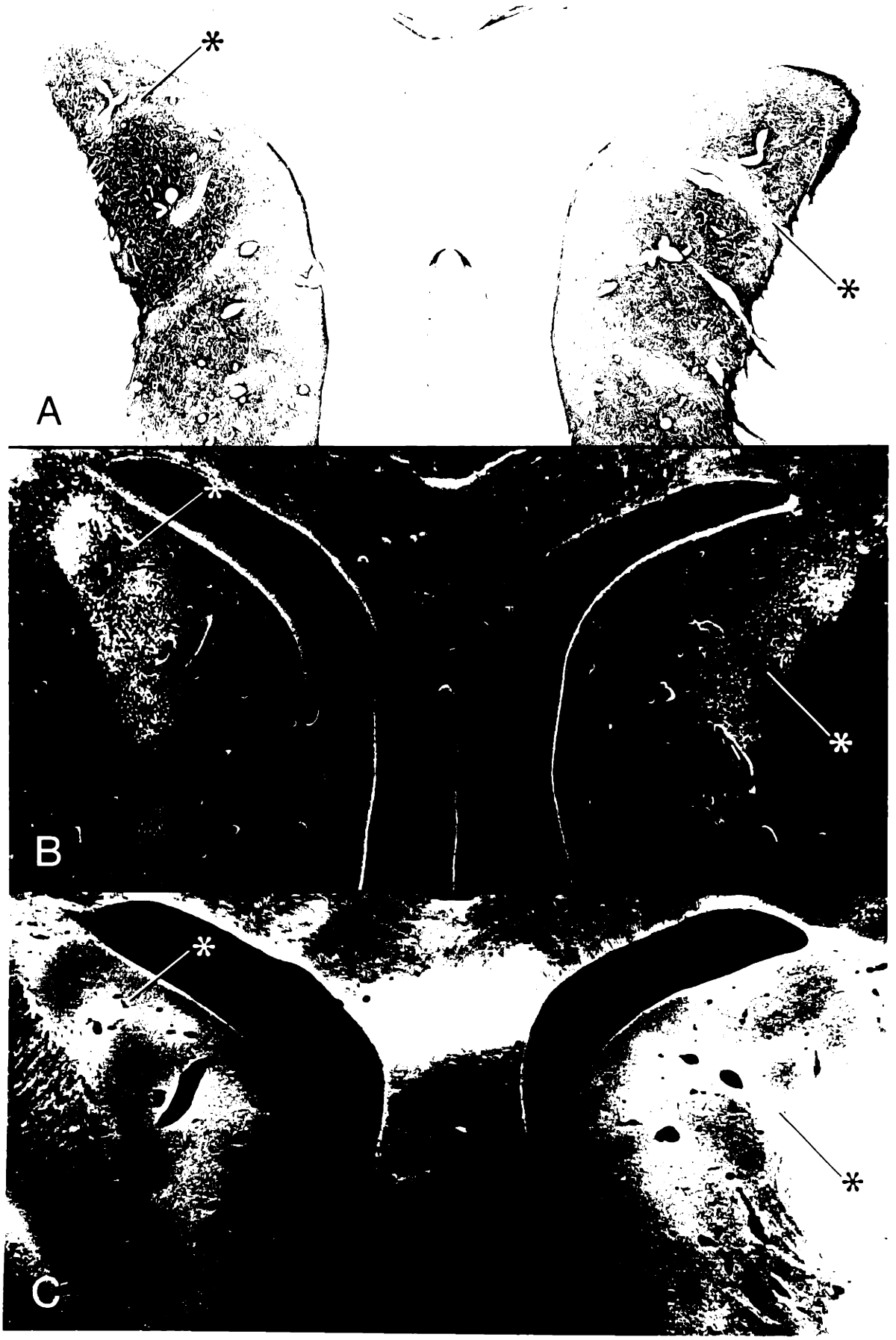
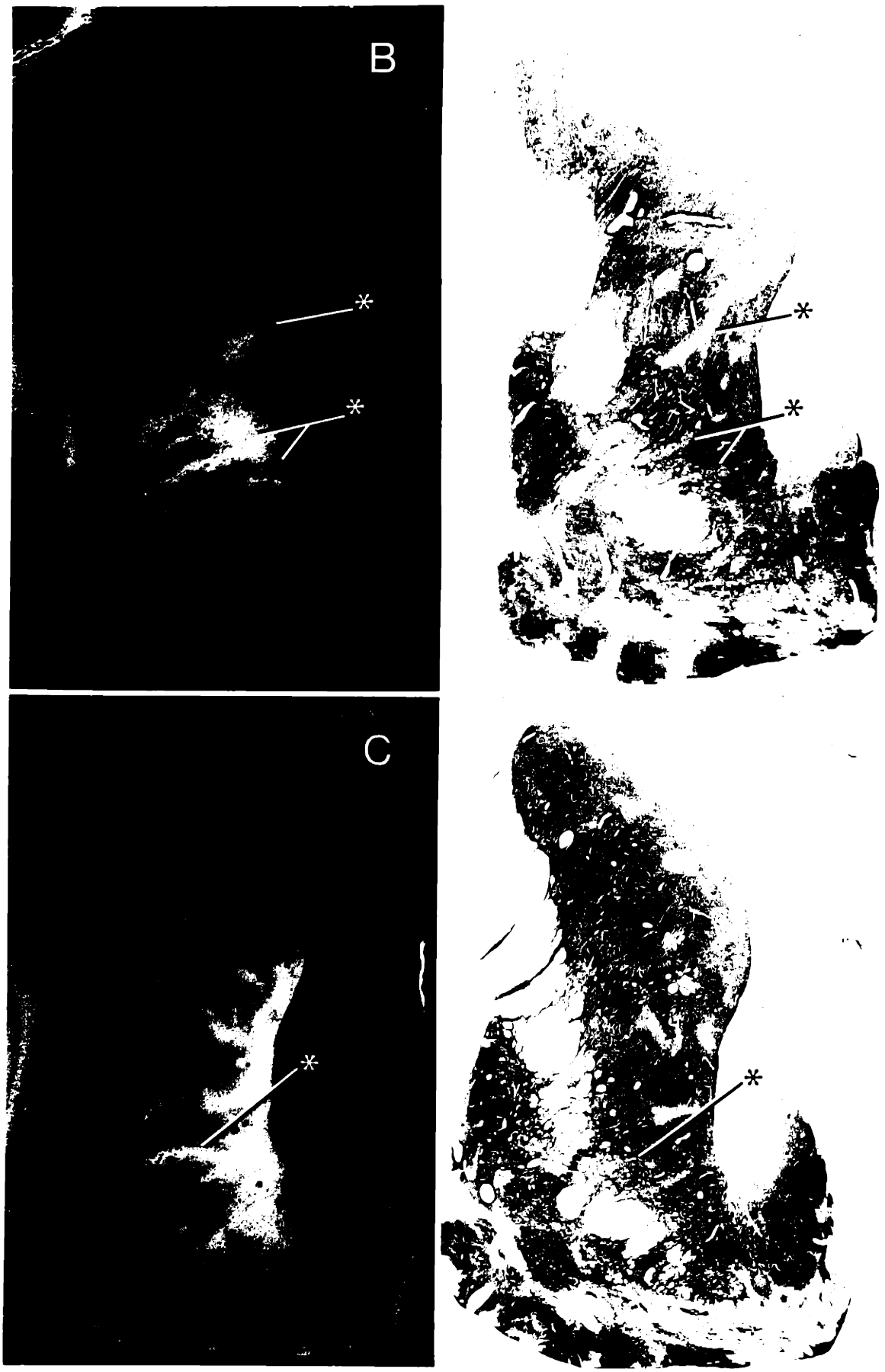

CRCx-38L
CRCx-38R
CRCT-1R
CRCx-24
CRCx-16
CRCT-2L
CRCx-44R
CRCx-11
CRCx-4L
CRCx-37

Figure 6-12: Patterns of fiber-labelling observed in the striatum following isotope deposits in insular (A,B) and rostral temporal (C) cortices. A: Broad inhomogeneous labelling of caudate nucleus in insular case CRCT-1R. Exposure time for autoradiogram: 25 weeks. B: Nearby serially adjoining sections taken from case CRCT-1R. Asterisks indicate that radiolabelled fibers (left) fill AChE-poor striosomes (right) throughout all but the base of the caudate nucleus, where matrix tissue is selectively innervated. Exposure time: 4 weeks. C: Fibers labelled in rostral temporal cortex case CRCT-2L fill AChE-poor striosomes in ventral caudate nucleus, including at the base of the nucleus (asterisks). Abbreviations: AC, Anterior commissure.


A
B
C


B
C

paralaminar ventroanterior nuclei, in the mediodorsal nucleus and in the lateral medial-supragenicuiate (LM-Sg) nuclear complex. There was a rostrocaudal shift across the cases in basolateral amygdala labelling with rostral deposits, such as in case CRCT-1R, presenting selective, heavy labelling of the basolateral nucleus and restricted labelling of the rostrocentral lateral nucleus, and caudal deposits, such as in case CRCx-24, strongly labelling the lateral nucleus and showing much reduced basolateral nucleus labelling, which was largely restricted to its dorsolateral corner.

Two cases that involved cortex caudal to the limits of the insula as defined by its contiguity with the claustrum, showed a pattern of striatal labelling similar to that of the insula. The injection site in case CRCx-38R embraced the cortex around the caudal end of the pseudosylvian sulcus (Fig. 6-11) and produced matrix labelling near the base of the caudate nucleus that avoided the striosomal compartment, and striosome labelling dorsally. Unlike more rostral deposits into the insula, the thalamic labelling in this case was completely restricted to the posterior thalamus- the LM-Sg complex and also the medial division of the lateral posterior nucleus (LPm) and parts of the medial geniculate body. The injection site in case CRCx-4R included the auditory area AII and the cortical territory ventral to it. Striatal fiber-labelling was barely detectable throughout most of the head of the caudate nucleus. The caudal head and rostral body, though, were well-labelled, with striosomes 'filled' dorsally and 'avoided' ventrally. It seems likely that this projection originates in the region ventral to area AII as control deposit CRCx-12, largely restricted to area AII, did not produce such labelling (see below).

Rostral Temporal Cortex

Selective labelling of ventral striosomes was elicited after deposits of tracer into the posterior sylvian gyrus or the cortex ventral to the terminus of the posterior ectosylvian sulcus. In case CRCT-2L, we blanketed most of the posterior

sylvian gyrus with tritiated proline and leucine. The deposits also covered the rostral pole of the gyrus and extended into the posterior agranular insula area, posterior prepiriform cortex and rostral area 36 (Fig. 6-11). The pattern of the striatal labelling seen in this case is illustrated by Figures 6-12 and 6-16/6. Striosomes were strongly labelled in the ventral caudate nucleus. There was also significant labelling of matrix tissue. Even though the matrix innervation was particularly pronounced ventromedially and at the base of the caudate nucleus, the labelling of striosomes was heavier, indicating a preferential innervation of striosomes by rostral temporal cortex in a striatal zone where fibers from insular cortex predominately terminate in matrix. The dorsal division of the nucleus accumbens was labelled after every deposit in rostral temporal cortex, and in case CRCT-2L there was also labelling in the olfactory tubercle.

Case CRCx-11, the injection site of which was centered somewhat more caudally in the posterior sylvian gyrus, also presented selective labelling of ventral striosomes, including those at the base of the caudate nucleus. This case differed from CRCT-2L in that labelling of the matrix compartment of the rostral caudate nucleus was less pronounced and did not include the tissue adjoining the ventricular face of the nucleus.

Temporal cortex ventral to the posterior ectosylvian sulcus was injected in four cats. In case CRCx-13, the deposit was placed at the base of the hemisphere and involved area 36. The three other sites were centered in the cortex just below and slightly behind the sulcus, that is visible in a lateral view of the hemisphere (see, for example, case CRCx-37 in Fig. 6-11). Striosomes were selectively labelled in these experiments. Their innervations, though, were not as crisp as those observed after more rostral deposits, and tended to be somewhat more fibrous and diffuse. In addition, the labelling of ventralmost caudate nucleus at caudal levels

tended to be rather even. These tendencies were most marked in case CRCx-3L, which also presented several candidate 'avoids' of striosomes in caudoventral caudate nucleus. Although the injection site in CRCx-3L did not appear positioned significantly caudal to that of CRCx-37, the presence of labelling features more typical of caudal temporal cortex (see below) suggests that the cortex ventrolateral to the base of the posterior ectosylvian sulcus represents a territory of transition.

These rostral temporal cases shared heavy labelling of the lateral nucleus of the amygdala, which was most dense rostrolaterally. The dorsolateral part of the basomedial nucleus and the lateral central nucleus were also labelled. Labelling of the basolateral nucleus, where noted, favored the dorsolateral part of the nucleus. In the thalamus, fibers were located along its posteromedial margin, in the medial geniculate complex, and along the subparafascicular nucleus-peripeduncular area continuum. In case CRCT-2L, there was also labelling of the medial part of the mediodorsal nucleus.

Comment. Selective innervation of striosomes was demonstrated following tracer-deposits within a broad, apparently continuous expanse of cortex that includes all of prefrontal cortex as well as insular and rostral temporal cortex. This projection to striosomes appeared spatially organized in that (1) deposits in different parts of cortex led to labelling of striosomes in different parts of the striatum and (2) the shifts in the locations of the striosomal labelling systematically followed shifts in the positions of the cortical deposits. The structure of this corticostriatal projection-system was, however, more complex than a straightforward, topographic projection to striosomes: except for those cortical regions that innervated striosomes at the base of the caudate nucleus- that is, ventromedial prefrontal and rostral temporal cortices, the striosome-projecting cortex engaged in a dorsal fill-ventral avoid pattern of innervation. This dorsal fill-

ventral avoid arrangement was, in fact, a common and robust feature of the case-material. It was present in twenty-six cortical experiments, and in no case in this series did we see either dorsal fills or ventral avoids alone, or the obverse pattern: ventral fills with dorsal avoids.

Innervation of the matrix compartment was observed in all of the cases reviewed, either as the ventral part of a dorsal fill-ventral avoid termination-pattern or, as in the example of rostral temporal input, as an innervation of matrix tissue that is reduced in comparison with the innervation of striosomes in the same striatal territory. With the exception of the input from motor cortex, this matrix innervation was fairly homogeneous and did not show any sub-compartmental organization.

PART III

Dorsal Posterior Ectosylvian Gyral Cortex

A good introduction to the kinds of innervation-patterns observed in this third collection of cases is offered by the striatal projections of the dorsal posterior ectosylvian gyrus. Deposits of radiolabelled amino acids were placed in this cortex in three cats (Fig. 6-11). A representative pair of sections, taken from case CRCx-38L, is illustrated in Figure 6-13A. The labelling elicited in the striatum occupied its central province, running from dorsomedial to ventrolateral caudate nucleus, and extended through the putamen at caudal longitudes. Included in the labelling-pattern are restricted zones of dense label, which were wholly contained within matrix tissue and were apparently unrelated to the striosome/matrix borders. While most of the other inhomogeneities in striatal labelling, particularly those in the ventral two-third's of the nucleus, were due to cortical fibers avoiding the striosomes, not all fiber-labelling was restricted to the matrix compartment. Particularly in the dorsal half of the nucleus, some of aggregations of labelled fibers

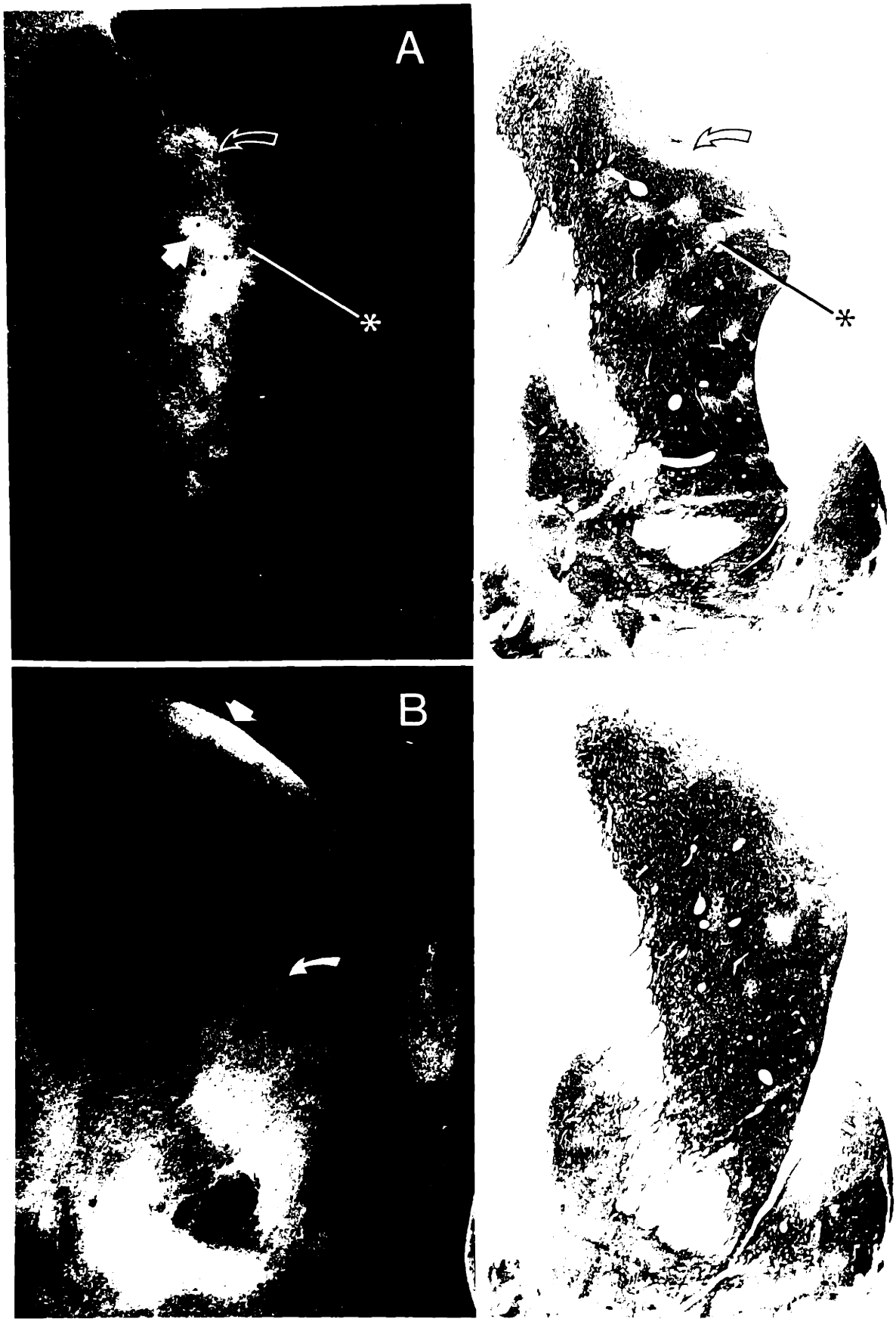
had an inhomogeneous, but not sharply defined, pattern of distribution. Comparisons of serially adjoining sections established that these inhomogeneities sometimes included striosomes in their field of distribution. In no instance, however, were crisp 'fills' of the caliber of those described in Part II, ever observed. Interestingly, in the caudal striatum, this inhomogeneous fiber-labelling appeared to condense into better defined patches, and these too sometimes overlay the striosomes.

The bulk of the injection site in case CRCx-38L lay within the area 7-recipient cortex of the dorsal posterior ectosylvian gyrus as defined in case CRCx-8 (see Part I). The remainder of the deposit extended somewhat rostroventral to this district. Trans-cortical labelling in this case included strong labelling of the insula, the lateral prefrontal cortex, the cingular area, area 7p, the lateral bank of the suprasylvian sulcus, caudal visual areas and parts of temporal cortex. There was broad labelling of the posterior thalamus, including both AChE-poor and AChE-rich districts of the LM-Sg complex. There was also labelling in some nuclei of the medial geniculate body. In the rostral amygdala, there was pronounced labelling of the lateral central nucleus and the panhandle and dorsolateral quadrant of the lateral nucleus. From the overall pattern of labelling, our deposits appear to have been centered in the para-visual region of the posterior ectosylvian gyrus, but to have significantly encroached upon the more anterior, para-auditory zone (area DP of Reale and Imig, 1980; see also Bowman and Olson, 1986).

Ventral Posterior Ectosylvian Gyral Cortex

Tracer-deposits were placed in the ventral posterior ectosylvian gyrus in cases CRCx-4L and CRCx-44R. In case CRCx-4L (Fig. 6-11), the striatal labelling was heaviest in the medial and ventral caudate nucleus. Its compartmental organization shared, however, many of the features of the dorsal posterior

Figure 6-13: Relation between labelled fibers (left) and AChE histochemistry (right) seen in autoradiographic experiments of caudal temporal cortex projections. A: Labelling principally avoids striosomes in ventral two-third's of the caudate nucleus (asterisk) and is sometimes arranged as dense patches within matrix (filled arrow). In dorsal caudate nucleus, labelling does not always respect the histochemical compartments, and labelled fibers reach striosomes (curved open arrow) as well as matrix. From dorsal posterior ectosylvian gyrus, case CRCx-38L. B: Labelling is dense along the dorsal quarter of periventricular caudate nucleus (short broad arrow) and in striatal tissue next to the anterior commissure. Labelled fibers are inhomogeneously distributed through central caudate nucleus, have access to the AChE-poor striosomes (curved arrow), but show no constant compartmental affiliation. From perirhinal area 35, case CRCx-32L.


A
B

ectosylvian gyrus projection: labelled fibers predominately avoided AChE-poor striosomes in the dorsal striatum and SP-rich zones in the dorsal division of the nucleus accumbens. Particularly in rostral caudate nucleus, the striatal innervation included patches of dense fiber-accumulations that, though similar in size and shape to the striosomes, were restricted to matrix tissue. In general, the 'avoids' were not well-defined, and it was common for labelled fibers to reach into striosomes, especially dorsal ones.

The injections in case CRCx-44R were placed somewhat rostral and dorsal to those of case CRCx-4L. The striatal labelling was largely similar, except that there were several compelling examples of labelled fibers specifically innervating striosomes. It seems possible that this striosomal input was due to injection site involvement of the caudal end of striosome-projecting, rostral temporal cortex.

These deposits in caudal temporal cortex were *not* distinguished from the rostral ones in their amygdalar connections: the lateral nucleus was heavily labelled and there were projections to the lateral central nucleus, the rostral basomedial nucleus and the dorsolateral part of the basolateral nucleus. The posterior thalamic connections of case CRCx-44R did, however, differ from those of the rostral temporal cortex; for example, projections to the LM-Sg complex were broadly distributed and not restricted to its medial margin. No caudal levels were available for study in case CRCx-4L.

Rhinal Cortex

The striatal projections of rhinal cortex located at, and caudal to, the level of the posterior ectosylvian sulcus were explored in five cats. In case CRCx-32L, a massive deposit of tritiated proline and leucine was placed in area 35 of the perirhinal cortex. The injection site somewhat infiltrated into laterally adjoining area 36 and the medially adjoining dorsal lateral entorhinal area (nomenclature of

Krettek and Price, 1977b). Figure 6-13B depicts the striatal labelling seen in this case. Labelled fibers were distributed broadly in the caudate nucleus, but collected densely in two sites: in caudate nucleus tissue adjoining the dorsal quarter of its ventricular surface and in the ventrolateral caudate nucleus, ventromedial putamen and nucleus accumbens tissue near to the anterior commissure. Except for the ventrolateral caudate nucleus, where perirhinal cortex strongly innervated both compartments, it was difficult to score the projection with respect to the striosomes, even though the labelled fibers were clearly inhomogeneously distributed. Fibers often did run through the striosomes (see example in Fig. 6-13B), but no selective compartmental affiliation could be established. Interestingly, the strong impression taken from this case was that the labelled fibers tended to collect near the striosomes.

In three experiments, the dorsal lateral entorhinal area and adjoining part of the ventral lateral entorhinal area were injected with radiolabelled tracers. The overall distribution of the striatal labelling seen in these experiments was quite similar to that described for the perirhinal case, but the overall density of the labelling was much reduced. Consequently, it was only possible to compare the labelled projection with the striosomes in the ventrolateral caudate nucleus. There, the labelled fibers appeared to innervate both compartments.

The deposits in rhinal cortex elicited strong labelling of the lateral central and basolateral nuclei. Pronounced labelling of the lateral nucleus was observed only in the perirhinal case.

Comment. Deposits placed in caudal temporal association cortex primarily elicited labelling of matrix tissue. The pattern of innervation was much more complex than that described for other regions of association cortex and could not always be successfully related to the histocompartmental architecture. Of particular

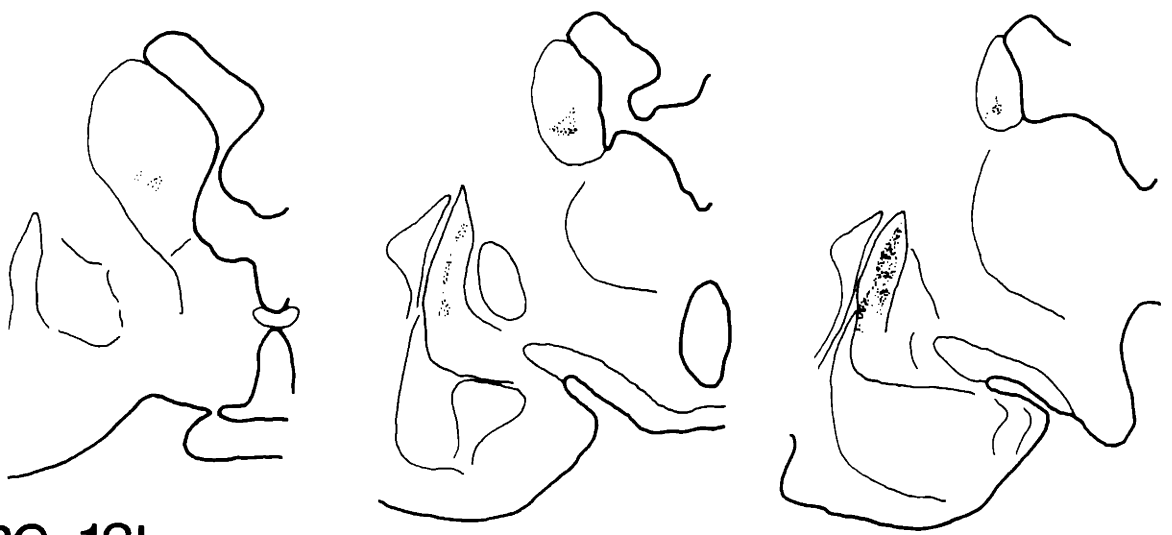
note was the often patchy quality to the innervation of the matrix, a feature which this input shared with the projections of sensory cortices (see below).

Sensory Cortices

Deposits in visual cortex. We did not investigate the striatal connections of areas 17 and 18 because in the cat, as in the primate (Kemp and Powell, 1970; Graham et al., 1979), these connections are either weak or non-existent (review of unpublished case-material of D.M. Berson). Visual area 19, however, is known to project to the striatum in the cat (Squatrito et al., 1981), and is early enough in visual processing to have an extensive representation of the visual field (Tusa et al., 1979). We investigated the organization of this projection in case CHRC-13R by making deposits of distinguishable tracers into its upper and lower field representations as identified by sulcal landmarks in the studies of Tusa and colleagues (Tusa et al., 1981). ^{35}S-Methionine was delivered to the medial bank of the middle part of the horizontal limb of the lateral sulcus (area 19 lower visual field representation) and HRP-WGA was injected in the anterior bank and adjoining gyral surface of the posterior descending limb of the lateral sulcus (area 19 upper field representation). The injection sites, though large, did not appear to involve adjoining visual areas significantly, and the cortical and subcortical distributions of labelled fibers confirmed that the tracers were restricted to distinct, upper and lower visual field representations. The basal ganglia projections of area 19 were confined to the caudal striatum and were organized as multiple circumscribed patches, even when the tracer was restricted to a part of the visual field (Fig. 6-14). At the level of the crossing of the anterior commissure, labelled patches were evident in the dorsal cap of the caudate nucleus. Caudally, the patches shifted dorsolaterally in the nucleus and entered the lateral margin of the putamen. They could be followed in these positions to the caudal end of the

Figure 6-14: Chartings of labelling observed in caudal caudate nucleus following tracer-deposits in visual area 19 (case CHRC-13R) and auditory area AI (case CHRC-13L). In the area 19 case, separate deposits of distinguishable tracers were placed in the upper and lower visual fields representations. The striatal labelling elicited is illustrated, respectively, in stipple and solid inking.

CHRC-13R



CHRC-13L

putamen. The fiber-patches labelled from the separate visual field representations did not overlap, nor were they intermingled, suggesting at least some degree of retinotopic segregation in the area 19 representation in striatum.

The striatal connections of four additional retinotopically organized visual areas were studied with autoradiography. Each of these areas innervated the area 19-recipient sector and strongly favored the caudal third of the striatum in the overall distribution of their projection-fibers, but the areas differed in the extent of their labelling of additional striatal districts. Case CRCx-15, in which a large deposit of isotope was placed in visual area 20a of Tusa and Palmer (1980), presented the most restricted striatal labelling: fibers innervated essentially the same striatal territory as area 19, although the volume of its termination dorsomedially in caudal caudate nucleus appeared somewhat greater. In case CRCx-39L, we made multiple injections of ^{35}S-methionine in the caudal half of the medial bank of the middle suprasylvian sulcus in an attempt to label fully the Clare-Bishop area of Sherk (1986). (Although Sherk's parcellation of the lateral suprasylvian visual areas differs conspicuously from that of Tusa and colleagues (1981), the bulk of her Clare-Bishop area corresponds with much of their PMLS area). In contrast to previous cases, there was prominent, though not heavy, labelling of dorsomedial and central parts of the caudate nucleus at mid-anteroposterior levels. In addition, labelled fibers could be detected in the dorsomedial caudate nucleus to the anterior head of the caudate nucleus. The striatal labelling was inhomogeneous, and correlative histochemical analysis established (1) that the labelled fibers avoided AChE-poor striosomes in central caudate nucleus and (one example) caudal putamen; and (2) that the matrix tissue was innervated in a patchy manner. It seems unlikely that the labelling of rostral caudate nucleus was due to injection site spread into adjoining posterior parietal

cortex as none of the transcortical connections that distinguish parietal from lateral suprasylvian cortex, such as those with the cingular area and area 6m (Olson and Lawler, 1987), were observed in case CRCx-39L.

In experiment CRCx-39R, the posterolateral bank of the suprasylvian sulcus was blanketed with ^{35}S-methionine. The striatal labelling elicited was not only heavier than that seen in the Clare-Bishop experiment; it extended from dorsomedial caudate nucleus well into the ventral half of the nucleus. At caudal levels the ventral caudate nucleus labelling was extremely dense. The compartmental pattern of the labelling was very similar to that described for the dorsal posterior ectosylvian gyrus cases: in the ventral half to two-third's of the caudate nucleus, the projection selectively innervated matrix tissue in an inhomogeneous fashion. Particularly in dorsal caudate nucleus, though, labelled fibers were not restricted to the matrix, but had access to the striosomes, and, in a few instances, fibers were observed to collect over AChE-poor striosomes. The injections site in case CRCx-39R covered the PLLS visual area of Tusa and co-workers (1981) (Tusa et al., 1981) and involved the adjoining cortex of the upper part of the lateral bank of the suprasylvian sulcus. J. Rose (1949) distinguished this cortex on cytoarchitectural grounds and designated it the suprasylvian fringe. Based on evoked potential studies, the suprasylvian fringe has been placed with the auditory system (Woolsey, 1959; see also Reale and Imig, 1980). The striatal connections noted in this case may therefore not be indicative of the output of a purely visual cortical region.

A large deposit of radioactive tracer was placed in the cortex ventrolateral to the posterior terminus of the suprasylvian sulcus in case CRCx-16 (Fig. 6-11. The resulting injection site occupied the rostral half of visual area PS, as described by Updyke (1986). Fiber-labelling was moderate through the center of the caudate

nucleus, and was particularly dense ventrolaterally and along the dorsal third of the ventricle. The labelled fibers principally innervated matrix tissue, but did not always respect the compartmental boundaries. The matrix innervation was inhomogeneously organized. Thus, the topographic and compartmental organization of the labelled projection to striatum appeared to be an amalgam of the patterns seen in the perirhinal and dorsal posterior ectosylvian gyrus cases, suggesting that area PS may be not only physically, but also connectionally intermediate between these cortical sectors (see also transcortical findings of Guldin and Markowitsch, 1984). From the retrograde tracing data of Royce (1982), it is clear that area PS projects in some volume to the striatum. The possibility, though, that a part of the observed labelling was due to involvement of areas beyond PS can not be excluded: our injection site did not appear to invade perirhinal cortex significantly, but we did observe anterograde label over area SII in this case, and Burton and Kopf (1984) have reported labelled cells in perirhinal area 36, and not area PS, following deposits of retrograde tracers into SII.

Deposits in auditory cortex. In case CHRC-13Lr, we blanketed auditory area AI, as mapped in the physiological experiments of Reale and Imig (1980), with ^{35}S-methionine. Labelled fibers were observed in caudal striatum, where they extended from the ventrolateral caudate nucleus through the middle third of the putamen (Fig. 6-14. In the same hemisphere, we injected HRP-WGA into auditory area P, which adjoins area AI caudally (Reale and Imig, 1980). The resulting injection site did not overlap the AI deposit, but did appear to extend into ventrally adjoining auditory area VP (Reale and Imig, 1980). Serial section comparisons demonstrated that the radiolabelled AI projection was coextensive with the enzymatically labelled P-VP projection. This suggests that the auditory system, like the visual system, has a striatal territory to which several areas

involved in early sensory processing project. As the chartings in Figure 6-14 suggest, the auditory zone adjoins the visual zone ventrally and medially (see also work in the squirrel by Lin et al., 1984).

The striatal projections of area AII, investigated in case CRCx-12, also reached the AI-recipient sector of caudal striatum, but were more extensive in central and ventral parts of the caudal caudate nucleus. Comparisons with the histochemistry established that the AII projection to caudal caudate nucleus avoids AChE-poor striosomes.

Deposit in olfactory cortex. In case CRCx-18, a large deposit of tritiated amino acids was placed in the anterior prepiriform area. The striatal labelling elicited was restricted to the ipsilateral olfactory tubercle. Labelled fibers were densest laterally, where they were distributed to the deeper cellular layers as well as to the deep half of the molecular layer ('layer Ib'). Labelling in the central part of the tubercle was not as heavy and was located mainly in the molecular layer. Those few labelled fibers observed in the medial olfactory tubercle were restricted to layer 1 and appeared to be in transit to the taenia tecta and the dorsal peduncular cortex (see also Haberly and Price (1978) and Luskin and Price (1983) in the rat). In the lateral olfactory tubercle, the cortical zones were much more heavily labelled than the cap zones (nomenclature of Meyer and Wahle, 1985).

Comment. Projections from visual and auditory cortices involved in the earliest stages of sensory processing terminate in caudolateral caudate nucleus and putamen, striatal sectors where striosomes are rarely demonstrated by histochemical methods. If this rarity reflects a problem in detection, then no conclusion about the compartmental target of these fibers is possible. If, as seems more likely, the cause is the infrequency of striosomes in this striatal region, then by their volume these sensory projections predominately reach matrix tissue.

Support for this view comes from two quarters. First, in the rat, primary visual cortex does not innervate striosomes identified by opiate binding autoradiography (Donoghue and Herkenham, 1986). Second, we were able to confirm selective innervation of the striatal matrix for two areas thought to be intermediate in the chain of sensory areas: the Clare-Bishop area of the visual system and auditory area AII. Interestingly, cortical regions that appear on anatomical grounds to participate in late stages of sensory processing, such as the dorsal part of the posterior ectosylvian gyrus and the lateral bank of the suprasylvian sulcus (Woolsey, 1959; Bowman and Olson, 1986), may have some access to the striosome compartment in dorsal caudate nucleus.

The observations in the area 19 case, that tracer-deposits in restricted parts of the sensory map lead to the labelling of multiple fiber-patches in the striatum and that fiber-patches labelled from different parts of the sensory map are essentially non-overlapping, are in accord with similar findings, also made in cat, for striatal projections of primary auditory and somatosensory cortices (Reale and Imig, 1983; Malach and Graybiel, 1986). However, a conclusion of a retinotopic organization in the area 19-recipient zone of the striatum, comparable to the somatotopic organization described in the somatic sensory-recipient sector of the striatum (Malach and Graybiel, 1986), is premature. We did not examine subareal topography for the other sensory cortices we studied, but our findings for outlying visual areas and for somatic sensory area SII (results not described) suggest that inhomogeneous ('patchy') innervation of matrix tissue is a common feature of striatal input from sensory cortex.

Discussion

In this chapter we have surveyed the compartmental organization of the corticostriatal projection in the cat. Our findings fall into three broad areas. First, we have tested the relationship between corticostriatal projections and striatal compartmentalization by making large deposits of anterograde tracers in a number of cortical areas. Our observations indicate that most cortical areas respect the compartmental structure of the striatum in their fiber-distributions. Second, we have established that projections to striosomes, like those to matrix tissue, arise from a large expanse of cortex and are spatially organized. As a consequence, for each district of striatum there is a characteristic set of afferent connections for the striosome and matrix compartments. Third, we have presented evidence that some regions of cortex display a dual pattern of compartmental innervation. From this last finding flows a novel analysis of the relationship between striosomes and matrix, one based on the structure of corticostriatal connections. This analysis will be presented below.

Inhomogeneities in the corticostriatal projection

We placed deposits of radiolabelled tracer in nearly every region of cat neocortex, including sensory and motor cortices, parietal, temporal, frontal, insular and medial limbic association cortices, and the cortex of the caudal rhinal sulcus. The labelling elicited in the striatum was in every case inhomogeneously patterned, suggesting that this is a universal feature of corticostriatal connections. A remarkably large amount of this heterogeneity could be explained by labelled fibers selectively affiliating with one or the other of the histochemically defined compartments of the striatum. Nearly all of the fiber-patterns seen in the projections from parietal, cingulate, frontal, insular and rostral temporal association cortex could be accounted for by the arrangement of striosomes within

the striatal matrix, and at least some of the fiber-distributions from caudal temporal and sensory association cortex was due to preferential fiber-termination in matrix tissue.

The arrangements of the histochemically defined compartments could by no means predict all corticostriatal inhomogeneities. First, the pattern of striatal fiber-labelling from parts of caudal association cortex did not always respect the striosome-matrix boundaries; labelled fibers that predominately reached matrix tissue would freely invade the striosome compartment. This problem in relating fiber-labelling to the histochemistry was particularly acute in the caudal rhinal cortex cases. The only conclusion possible with this material was that fibers are not restricted to either compartment, but that they appear to prefer to terminate in the vicinity of striosomes.

Second, there were inhomogeneities in striatal fiber-labelling that were wholly restricted to one histochemical compartment, specifically the matrix. Compelling evidence for matrix heterogeneity in the corticostriatal system was first documented in a study of somatic sensory projections in cat (Malach and Graybiel, 1986; see also Reale and Imig, 1983; Donoghue and Herkenham, 1986). These workers found that tracer injections restricted to areas SI or 3a elicited multiple, circumscribed patches of labelled fibers in the dorsal putamen and dorsolateral caudate nucleus. These patches were confined to the matrix compartment and their profiles could not be predicted from the positions of the striosome-matrix boundaries. Our observations indicate that inhomogeneous matrix projections hold for cortical areas not just at early, but also late stages of sensory processing. Furthermore, matrix inhomogeneities are limited neither to the projections of sensory-affiliated cortical areas nor to particular striatal sectors: patchy matrix labelling was elicited in ventral and medial caudate nucleus following deposits

placed in the ventral posterior ectosylvian gyrus (*e.g.*, case CRCx-4L in Fig. 6-11). These observations for the corticostriatal system, that some but not all components of this system project inhomogeneously to extrastriosomal matrix tissue, are in line with findings for both the thalamostriatal and amygdalostriatal connections. The matrix inhomogeneity we saw in the amygdalostriatal connection was restricted to the ventral caudate nucleus, but patchy thalamostriatal input, like that from cortex, can apparently be found in all sectors of dorsal striatum (see Chapters 4 and 5). Interestingly, the matrix patches we have seen in central caudate nucleus after appropriate cortical and thalamic deposits appear to be larger than those observed in the somatic sensory- and area 19-recipient sectors of the striatum. This would fit with the observation that striosomes in dorsolateral caudate nucleus and caudal striatum, as identified by SP immunohistochemistry, are smaller than those observed more centrally in the striatum, and the suggestion that the size and shape of both striosomes and extrastriosomal matrix patches may be determined by the nature of the striatal sector in which they lie (Malach and Graybiel, 1986).

In double labelling experiments, Malach and Graybiel (1986) demonstrated that the SI and 3a matrix patches do not overlap but interdigitate. This suggests that the matrix of the somatic sensory-recipient sector of the striatum has a spatially specified mosaic structure whose functional basis is, in part, submodality segregation. It would be of great interest to identify cortical areas that interdigitate in their projections elsewhere in the striatum, for example, in central caudate nucleus, as this might suggest a segregation of functional processes within other parts of the striatal matrix[8]. These investigations are beyond the scope of this thesis. Consequently, we can not conclude that the matrix inhomogeneities

[8]A possibility here is that modality-specific segregation of the projections of the para-visual and para-auditory zones of the dorsal posterior ectosylvian gyrus might occur in central caudate nucleus (Bowman and Olson, 1986).

observed in central and ventral caudate nucleus reflect a spatially specified mosaic structure similar to that of the somatic sensory sector, and not, say, a more fluid arrangement of partially overlapping zones of matrix input.

The corticostriatal projections we have described in the fall into three classes, constructed according to type of inhomogeneity observed: projections that include selective innervations of striosomes, projections that reach matrix tissue homogeneously, and projections that feature marked matrix heterogeneities (described in Parts II, I and III, respectively). The cortices that issue each of the projection-patterns appear to be physically continuous with one another, raising the possibility that, in terms of corticostriatal connections, the cortical mantle can be divided into three broad plates.

The striosome-projecting cortex extends from medial prefrontal cortex across the gyrus proreus and the praesylvian sulcus, through the region of the insula, to rostral temporal cortex. Our injection sites, taken together, cover much of this territory and thereby strongly support a claim of continuity. We do not have a similar march of deposits for the cortex that projects homogeneously to matrix tissue, but published cytoarchitectural maps suggest that parietal and cingulate cortices might merge across the splenial sulcus (Rose and Woolsey, 1948a; Hassler and Muhs-Clement, 1964; Olson and Jeffers, 1987). As for the inhomogeneous matrix-projecting areas: it is clear that caudal temporal association cortex is continuous with nearby visual and auditory cortices. The finding that the cortex of the lateral bank of the suprasylvian sulcus also participates in this pattern of innervation raises the possibility that the belt of parasensory association cortex that runs anteriorly through the suprasylvian sulcus to reach the anterior ectosylvian gyrus (Graybiel, 1972b) may offer a physical link cortex to the heterogeneous matrix-projecting sensory and motor cortices.

An obvious question is, what is the nature of the striatal projections of cortex situated where these plates meet? As we have noted, parietal cortex is not without hints of matrix heterogeneity, so a passage from, for example, the Clare-Bishop area to posterior parietal cortex may not be very marked. Our deposits in temporal association cortex and in medial prefrontal cortex (Figs. 6-11 and 6-5) suggest that the transitions there, between striosome-projecting cortex and matrix-projecting cortex (heterogeneous and homogeneous, respectively) are quite sharp[9]. Interestingly, the transition we have identified in medial prefrontal cortex apparently corresponds quite precisely with the border between limbic cortex and orbitofrontal cortex identified by Rose and Woolsey on the basis of cytoarchitecture and, *post hoc*, of thalamic connections (compare Figs. 6-3-top with 6-5). The division between rostral and caudal temporal cortex appears, on the other hand, to be a novel one, at least in cat.

We could not decide the status of all areas at regions of transition. Injections in, for example, motor cortex clearly elicited matrix inhomogeneities, but large deposits (which may or may not have involved premotor areas) also labelled striosomes. Similar problems plagued our observations on the connections of somatic sensory area SIV. We do not describe these cases in the results because we could not resolve whether the labelling observed, which was a mixture of SII (matrical) and insula (striosomal) projection-patterns, was due to involvement of multiple areas or a reflection of the intermediary position of area SIV.

Finally, we note that the principle that adjoining areas of cortex project to adjoining or overlapping areas of striatum appears to hold even across these

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[9]Recalling, however, that the striosome-projecting cortex ventral to the ventral posterior ectosylvian sulcus is not free of the features of caudal temporal cortex and that deposits in the caudal medial prefrontal cortex do appear to label significantly the matrix tissue of the ventromedial caudate nucleus.

compartmentally defined cortical boundaries. As examples, consider the transitions just reviewed. The Clare-Bishop area and the posterior parietal cortex both project dorsomedially in striatum, and caudal ventromedial prefrontal cortex and the 'prelimbic' cortex of the anterior limbic area, as well as adjoining parts of rostral and caudal temporal cortex, all project to ventral and medial caudate nucleus.

General distinctions between cortex that reaches striosomes and cortex that is restricted to matrix

In their study of the compartmental organization of corticostriatal connections in rat, Donoghue and Herkenham (1986) identified only one cortical area- prelimbic cortex, or area 32- that preferentially innervates the striosomal compartment (see also Gerfen, 1984). They commented that such a unique input for all striosomes should allow one to characterize the functional role of the striosomes, at least in part, by characterizing the cortical area in question. Noting that "connectivity studies suggest a 'limbic' function for prelimbic cortex", they indicated some 'limbic' function might distinguish striosomes from matrix tissue.

We have found that area 32 of the cat does not innervate striosomes, but restricts its fiber-distributions to matrix tissue. This discrepancy between the studies is almost certainly a technical problem of identifying homologous cortical areas. We followed Room et al. (1985) in calling the pregenual territory of the anterior limbic area of Rose and Woolsey (1948a) as prelimbic. Although Rose and Woolsey did not distinguish a prelimbic cortex, they did state that "[Brodmann's] areas 32 and 24 correspond closely to our anterior limbic field". Our finding that the caudal ventromedial prefrontal cortex immediately anterior to cat prelimbic cortex selectively fills striosomes strongly suggests that it is this cortex that corresponds to the rat prelimbic cortex studied by Donoghue and Herkenham. Thalamic labelling in our cases suggests that what sets cat area 32 apart from

adjoining prefrontal cortex is the predominance of anteromedial over mediodorsal nuclear labelling (Niimi et al., 1978; Niimi et al., 1981). Unfortunately, the only non-striatal connections of rat prelimbic cortex that Donoghue and Herkenham identify are projections to it from the amygdala. At least in cat, this anatomy does not distinguish prelimbic and prefrontal cortices. Recent findings in the monkey suggest that area 32 in that species is not connected with the anteromedial nucleus (Vogt et al., 1987), which would indicate additional problems of homology for cat 'prelimbic' cortex. Clearly, cytoarchitectural identification of areas in medial frontal lobe is not a reliable basis for homology, but thalamic and striatal projection-patterns may be. It is possible that, once appropriate connectional studies are done, an identification of pregenual medial limbic cortex in the cat as 'area 32' should be abandoned to bring cat cortical parcellations in line with those of rat and monkey.

The other differences we have with the findings of Donoghue and Herkenham (1986) are more fundamental. In the cat, projections to striosomes do not issue from a single cortical area, but from a broad expanse of tissue, stretching from medial prefrontal cortex to rostral temporal cortex. Moreover, this input to striosomes is spatially organized in that striosomes in different parts of the striatum receive input from different cortical regions. Characterizing what distinguishes cortex that innervates striosomes from that that is restricted to matrix tissue, is, then, a much more complex matter.

Nevertheless, certain general comments are possible. First, as Donoghue and Herkenham pointed out, primary sensory and motor input appears largely confined to the matrix, as are at least some association cortex projections. Thus, the differences in inputs to the striatal compartments are neither between sensory and motor processes, nor between early sensorimotor cortices and association cortex,

but must lie in aspects of association cortex function. Second, the differences do not appear determined by position in the sequence of cortical areas leading from early sensory to higher-order association cortices and into limbic cortex. It would, for example, be difficult to decide which of the posterior parietal cortex- which exclusively connects with matrix tissue- and granular insular cortex- which primarily innervates striosomes- is the higher-order area. Both, for example, are visually responsive, contain cells with receptive field properties of considerable complexity, and do not appear to be organized retinotopically (Benedek et al., 1986; Dubner and Brown, 1968; Olson et al., 1987).

The property that best captures the difference between striosome-targeted and matrix-targeted cortical areas appears to be their limbic system affiliations. Anatomical studies indicate that the limbic system at the level of cortex and thalamus is organized as two largely separable circuits (Nauta, 1962). The amygdala is the hub of one of these circuits, which consists of the basolateral complex of the amygdala, its main thalamic link (the medial division of the mediodorsal nucleus), and their shared targets in frontal and rostral temporal cortex. The hippocampal formation and its targets, particularly the fornix-afferented thalamus (including the anterior nuclei) and parts of the cingulate gyrus, compose the other circuit (Papez, 1937). These circuits are not autonomous- there are several sites of interconnection between these subsystems, including sectors of parahippocampal and anteromedial cortex (Krettek and Price, 1977b; Amaral, 1986; Rosene and Van Hoesen, 1977; Beckstead, 1976; Swanson, 1981); but this division has strong anatomical support and has recently proved essential for the interpretation of behavioral data on global amnesia in monkeys and humans with limbic system damage (Mishkin, 1978; Aggleton and Mishkin, 1983; Squire, 1981).

When the compartmental organization of cortical areas distinguished by their

limbic system links are examined, a dissociation is quite clear. Consider, first, the cortical regions with the most extensive and selective projections to the matrix or the striosome compartment; respectively, they are the cingulate cortex and the insular cortex. The cingulate cortex, of course, constitutes medial limbic cortex, and is yoked to hippocampal circuitry by, *inter alia*, its massive connections with the anterior nuclear group of the thalamus. The insular cortex is also considered a limbic-system structure (Yakovlev, 1959). It, however, is linked to amygdala-affiliated circuitry. It receives part of its thalamic input from the mediodorsal nucleus, but none from the anterior nuclei, and it projects heavily to amygdala.

Other cortical regions we have studied can also be associated, with varying degrees of success, to one of these two limbic circuitries. For example, rostral temporal cortex would, by its cortical and subcortical connections, be placed with amygdaloid circuitry, even though it also projects into entorhinal cortex (Van Hoesen and Pandya, 1975; Amaral et al., 1983)[10]. This accords with its principal striatal innervation being of striosome tissue. The compartmental organization of projections from frontal cortex are quite complex, but one finding is clear- ventral prefrontal cortex has the most selective affiliations with striosomes. The limbic system connections of frontal cortex also appear complex, but as analyzed by Nauta (1964): "... the orbitofrontal cortex appears to be connected mainly with the amygdaloid complex and related subcortical structures, [whereas] the dorsal half or so of the prefrontal convexity would seem to be associated more especially

[10]The differences between rostral and caudal temporal cortex is interesting in this regard. Both project to the amygdala and both send connections into the parahippocampal gyrus, which in turn leads to the hippocampal formation. The difference appears to be the rostrocaudal position of their entry to entorhinal cortex (Van Hoesen and Pandya, 1975). Rostral projections will reach principally the lateral entorhinal area, which also receives strong input from amygdala (Krettek and Price, 1977b). Caudal projections will pass through the medial entorhinal area. This part of entorhinal cortex receives no amygdalar input, but connects strongly with the presubiculum of the Papez circuit (Shipley, 1975).

with the hippocampal mechanism." Thus, cortex with more prominent links to the striosome compartment appears more strongly associated with amygdaloid circuitries (see also disposition of sectors of prefrontal cortex in striosomally-based ordering of cortical areas discussed below). Finally, even the matrix-projecting parietal cortex can be linked to limbic system circuitry. Direct projections have been traced from this cortex to the presubiculum of the hippocampal formation (Seltzer and Van Hoesen, 1979).

A linkage between striosomes and the amygdala was first indicated by our findings, reported in Chapter 4, that direct amygdalostriatal projections (and, most selectively, those from the basolateral nucleus) innervate striosomes in ventral and medial caudate nucleus. Taken with our suggestion that cortex that projects to striosomes may be distinguished by its affiliations with amygdala-related circuitry, it seems possible that the strength or specific organization of the direct corticoamygdaloid projection may be correlated with the compartmental organization of the striatal projection from that part of cortex. However, this is not the case. To give two examples: the anterior limbic area, which projects to matrix, connects strongly and specifically to the basolateral nucleus; and the transition between rostral and caudal temporal cortex, which is defined by a marked shift in the compartmental organization of the corticostriatal pathway, is not recorded in the corticoamygdalar connection. In brief, the corticoamygdalar pathway appears to reflect the *topography* of the corticostriatal projection; if the cortex projects to ventral and medial caudate nucleus, it will project in volume to the amygdala. The subnuclear specificity of the connection seems determined by the cortical lobe of issue- for example, the lateral nucleus connects strongly with temporal cortex, but more weakly with frontal cortex (Russchen, 1982a; Amaral and Price, 1984).

There appears, however, to be an association for given cortical areas between

their connections with specific striatal compartments and their projections to thalamus. A strong connection with fornix-afferented thalamus (including the anterior nuclei) apparently guarantees an exclusive affiliation with the matrix compartment. There is no comparable anatomy for striosome-projecting areas. For example, although many cortical areas that project to striosomes also project to the mediodorsal nucleus, mediodorsal connections are not made by most of the striosome-projecting rostral temporal cortex, but are by the matrix-projecting 'prelimbic' cortex. However, the mediolateral placement of thalamic connections does appear to predict both the presence and topography of connections with striosomes.

Projections directed laterally in thalamus, for example, by posterior parietal cortex to the pulvinar, are associated with input to the matrix. More medial connections, for example, to the ventromedial nucleus or to central mediodorsal nucleus, are found with cortex that projects to striosomes. And, within the mediodorsal nucleus, more medial thalamic labelling closely tracks more ventral striosomal labelling. The experiments with most ventral striosomal labelling, those in caudal ventromedial prefrontal cortex and rostral temporal cortex, are distinguished from all other cases by the extreme medial placement of their thalamic labelling- either in the mediodorsal nucleus in the prefrontal cases, or along the posterior thalamic border in the temporal experiments. This mediolateral organization appears to apply to connections with the lateral thalamic mass and mediodorsal nucleus; connections with the anterior group result in a projection exclusively to matrix.

It is possible that the respective limbic system affiliations of cortex connecting with the two striatal compartments may be reflected in their physical location. We noted earlier that the cortical areas that project to striosomes and those that

selectively innervate matrix tissue seem to cohere, and form distinct cortical plates. These plates meet in medial frontal lobe, from which the 'matrix' plate extends caudally and dorsally, running along the medial margin of the hemisphere, and the 'striosome' plate stretches rostrally and laterally, adjoining the hemisphere's lateral edge. Interestingly, a number of workers, most prominently Sanides (1970), have suggested on cytoarchitectonic grounds that the neocortex can be divided into two components, which appear somewhat similar to the compartmentally-defined plates. In Sanides' view, cortex is constructed of zones of progressively more highly differentiated isocortex, extending away from a focus of allocortex. There are two such foci, one associated with the hippocampal formation (archicortex); the other, with piriform cortex (paleocortex). Associated with the hippocampal focus is the medial limbic cortex of Rose and Woolsey, which we know connects solely with matrix, and extending from the piriform focus are orbital, insular and temporal polar cortices, which innervate striosomes. The account of Sanides is, of course, elaborate and detailed, but it principally concerns the primate, so further comparison is not possible. The test of any relationship between Sanides' cortical duality and cortical regions distinguished by their corticostriatal projections will be whether the "dividing line ... between the medial limbic zone of the influence and the insulolimbic zone of the influence" corresponds to zones of transition in the compartmental target of corticostriatal fibers.

This evidence that the distinction in limbic system between hippocampal and amygdalar circuitry may underlie the affiliation of cortical association areas with striosomes or matrix adds to our expanding understanding of limbic system involvement in striatal system function. This evidence does not, however, mean that striosomes are the limbic compartment of dorsal striatum. In fact, it means almost the opposite; from what we have described, matrix tissue, in virtue of its

affiliations with cingulate cortex, has as much status as a limbic compartment as do striosomes. Moreover, a 'limbic' compartment in dorsal striatum has already been identified on the basis of afferent connections from both arms of the limbic system; it is the ventral and medial caudoputamen (Kelley et al., 1982). To call striosomes 'limbic' is then to confuse a quite specific anatomy[11].

Our observations are not the first to indicate divisions in striatal tissue based on the limbic system dualism of hippocampus and amygdala. In ventral striatum, amygdalar fibers terminate densely in lateral nucleus accumbens, but only sparsely in a medial accumbens district to which fornix fibers are restricted (Kelley and Domesick, 1982). In dorsal striatum, a retrospective analysis of findings on the nigrostriatal projection indicates that the compartmental organization of this connection may also be specified, at least in part, by limbic system subcircuitries. Work in rat (Moon Edley and Herkenham, 1984; Gerfen et al., 1987) and cat (Jimenez-Castellanos and Graybiel, 1987) has shown that it is the pars compacta of the substantia nigra (cell group A9) that innervates the striosomes, and the outlying nigral districts of the retrorubral (A8) and ventral tegmental (A10) areas that provide midbrain input to matrix tissue. The ventral tegmental area is considered part of the limbic midbrain region in virtue of its limbic system input (Nauta, 1958); and its specific projections to ventromedial striatum helped to define this district as 'limbic-afferented' striatum (Kelley et al., 1982). For our purposes, the important point is that the identification of matrix-projecting medial midbrain as limbic was based on direct and indirect pathways from hippocampus- for example, connections with the septal region (Nauta, 1958; Valenstein and Nauta, 1959). By contrast, the limbic input to the striosome-projecting substantia nigra pars compacta arises principally from the amygdala and its affiliates (Krettek and Price, 1978a; Hopkins et al., 1981; Price and Amaral, 1981; Grove, 1987).

[11]See, for example, Gerfen et al., 1987.

Inputs to striosomes and matrix vary according to the striatal district considered

Our observations on the corticostriatal connection suggest that both compartments in every sector of striatum receive input from some region of cortex. Because given areas of cortex do not project throughout the striatum, but are restricted to specific regions, it follows that the histochemical compartments in each striatal sector will receive distinct and characteristic cortical input.

Sensory motor-recipient sector of the striatum. The main striatal targets of fibers from cat sensory-motor cortex are the dorsolateral head of the caudate nucleus and the dorsal half of the rostral putamen (Garcia-Rill et al., 1979; Malach and Graybiel, 1986; this chapter). Input to the matrix tissue of this striatal sector is provided by parietal cortex: fibers labelled by deposits in somatic sensory cortical areas SI, 3a and SIII (Malach and Graybiel, 1986), and anterior parietal association cortex avoid dorsolateral striosomes identified by AChE or SP histochemistry. By contrast, it is in the frontal cortex that the cortical innervation of these striosomes arises: labelling in striosomes of the sensory motor-recipient sector was observed after tracer-deposits centered either in area 6aβ on the anterior sigmoid gyrus or in the buried, lateral bank of the praesylvian sulcus.

Guitton and Mandl (1978a) have identified this praesylvian zone as the 'lateral oculomotor region', but it does not appear to be an area of primary oculomotor control comparable to the frontal eye field of the primate. The latencies of saccades evoked by electrical stimulation of this cortex are much longer than those elicited from the medial oculomotor region (which Guitton and Mandl suggest does resemble the monkey frontal eye field), and the principal kinds of saccade evoked were centering, or goal-directed, eye movements rather than movements whose amplitude and direction were independent of the position of the

eye in the orbit. Interestingly, neurons in the lateral area discharge not only with eye movements, but also in conjunction with movements of the neck, and this area's threshold for eliciting neck movements is low. From these findings, Guitton and Mandl (1978b) suggest that the lateral oculomotor area in fact "may act as a motor center for head movements," possibly one coordinating head and eye movements. The possibility that a cortical area that has access to striosomes in the sensory-motor recipient sector may function to coordinate the movements of different body parts, warrants further investigation.

The relationship of motor cortex fibers to the striatal compartments is a more complicated matter. Deposits of anterograde tracer in pericruciate cortex produced inhomogeneous labelling in the dorsolateral caudate and dorsal putamen, most of which reaches matrix tissue and avoids striosomes identified by AChE staining, SP-like immunohistochemistry and area 6 input. However, in case CRMC-4, in which a large deposit of ^{35}S-methionine was centered in area 4 and in which the peptide immunohistochemistry worked particularly well, we detected 'fills' of striosomes in the dorsal-most cap of the caudate nucleus. These were clearest along the medial and dorsal margins of the sensory motor-recipient district, and within the contralateral striatum. We could not establish fills in our other cases of motor cortex injections: in some cases the fiber-labelling did not extend far enough into the caudate nucleus and in other cases the histochemistry for the striosomes did not work well in this district. Although the injection site labelling in case CRMC-4 did not appear to infiltrate adjoining areas significantly, our experiments do not yet permit a conclusion that a dual pattern of compartmental innervation originates in area 4 and not in abutting premotor fields.

Our limited observations on motor cortex projections in the monkey are strikingly similar to those just noted in the cat (Ragsdale and Graybiel, 1984).

Corticostriatal fibers labelled by multiple deposits of tritiated amino acids in monkey area 4 not only innervated most of the putamen, but reached into the dorsolateral corner of the caudate nucleus (see also Kunzle, 1975). The labelling in the putamen was restricted to matrix tissue; in the caudate nucleus, though, label was concentrated in the striosomes. Thus, in the monkey as in the cat, large tracer injections centered in motor cortex elicited labelling of matrix throughout all of its striatal field of termination *except* the dorsal- and medial-most parts, where labelling was, instead, localized to striosomes. Unfortunately, we are no more sure in the monkey that this projection arises in motor cortex rather than in some adjoining premotor field. This point may be difficult to resolve because, even in monkey, a precise rostral border for area 4 is difficult to establish (Weinrich and Wise, 1982). Our findings suggest, though, that if motor cortex in the monkey projects to the dorsolateral caudate nucleus, then it also projects to striosomes.

Donoghue and Herkenham (1986) have examined motor cortex projections in the rat. In this species, fibers labelled by area 4 injections avoided the opiate receptor patches (striosomes) in their striatal field of termination except for the tissue along the lateral margin of the caudoputamen. There, the label clearly overlapped the opiate receptor-rich 'subcallosal streak'. While, topologically, the position of the overlap in the rat was not strongly similar to that of the 'fills' seen in cat and monkey, there is now evidence in three species for cortex within or adjoining area 4 having access to some striosomes.

If motor cortex participates in what is essentially a dorsal fill-ventral avoid pattern, then does any frontal cortex innervate matrix tissue in the striatal district where motor cortex fills striosomes? Our preliminary observations in the monkey indicate that the supplementary motor area (SMA) not only projects broadly through the dorsolateral caudate nucleus and putamen, but innervates matrix

tissue throughout (Ragsdale and Graybiel, 1984). A cat homologue to the primate SMA has not been identified, but the cortex of the caudal half of the dorsal bank and adjoining fundus of the cruciate sulcus (areas 4δ and 4sfu) is a promising candidate in virtue of its general position and connections with area 4γ, the medial reticular formation of the lower brainstem, and the spinal cord (Hassler and Muhs-Clement, 1964; Yumiya and Ghez, 1984; Berrevoets and Kuypers, 1975; Biedenbach and DeVito, 1980). Because of its inaccessibility, we were not successful in placing injections into this cortex.

Dorsocentral and dorsomedial caudate nucleus. As in dorsolateral caudate nucleus, parietal cortex provides input to matrix tissue and prefrontal cortex supplies afferent connections for the striosomes. However, the sub-regions of parietal and frontal cortex that project to dorsomedial caudate nucleus differ from those connecting dorsolaterally. Parietal inputs originate from posterior (visually affiliated) and not anterior (sensory motor-related) districts, and prefrontal connections are strong from the dorsal gyrus proreus. Additional districts of association cortex are also significant sources of dorsomedial caudate nucleus connections- the cingular area projects to matrix tissue and insular cortex reaches striosomes. Retrograde tracing studies indicate that area 6m along the ventral lip of the mesial cruciate sulcus projects strongly to dorsocentral and dorsomedial caudate nucleus (Royce, 1982; Kubozono et al., 1986). Unfortunately, in no case were we fully successful in confining a tracer-deposit to area 6m, as defined by the receipt of fibers from posterior parietal cortex (Heath and Jones, 1971b; Olson and Jeffers, 1987). Our experiments do, though, suggest that area 6m principally projects to matrix tissue of dorsocentral caudate nucleus, but innervates striosomes dorsolaterally and anteriorly within its striatal field of termination.

Consistent with the affiliation with visuomotor mechanisms that is suggested

by its input from posterior parietal cortex and from area 6m (which has been implicated in oculomotor function; Schlag and Schlag-Rey, 1970; Guitton and Mandl, 1978a), dorsocentral and dorsomedial caudate nucleus appear to receive input from sensory cortices involved in vision, such as the lateral suprasylvian visual areas and parts of caudal temporal cortex (Royce, 1982). Most of this input, for example, that from retinotopically organized zones such as the Clare-Bishop area, is directed to matrix tissue, but for some areas reached late in sensory processing there is also access to dorsomedial striosomes.

Ventral caudate nucleus. A description of the compartmental organization of cortical input to ventral caudate nucleus is complicated by the bicompartmental innervation-pattern of most of frontal cortex. However, a number of points that distinguish ventral from dorsal caudate nucleus are clear. Dorsal prefrontal cortex projects not to striosomes, but to matrix tissue. There is no input from early stages of sensory or motor processing, or from parietal cortex. Cingulate cortex and caudal temporal cortex, as well as very late stages of sensory-motor processing, provide additional connections for matrix. Input to striosomes is principally offered by cortex in ventral prefrontal and rostral temporal cortex that does not appreciably innervate dorsal caudate nucleus.

The anatomy of input to the base of the caudate nucleus is more straightforward: cingulate, insular, caudal temporal and most of ventral prefrontal cortex project to matrix. Only caudal ventromedial prefrontal and rostral temporal cortex selectively reach the striosomes.

Comparison with observations in the primate

A number of important conclusions about the organization of the corticostriatal connection have issued from anterograde studies in macaque monkeys carried out in the laboratories of P.S. Goldman-Rakic and G.W. Van

Hoesen (Goldman and Nauta, 1977; Selemon and Goldman-Rakic, 1985; Yeterian and Van Hoesen, 1978; Van Hoesen et al., 1981). Although these studies were not designed to relate the distribution of corticostriatal fibers to the arrangement of histochemical compartments, many of our observations can be related to their findings. First, we found in the cat that, as in the monkey, striatal projections from most all cortical areas are elongated in the anteroposterior dimension. Second, the striatal districts of termination of cortical areas linked by association connections do appear to overlap, at least in part[12]. For example, cross-case comparisons in the cat indicate that rostral temporal and ventral prefrontal cortex both project to the ventral caudate nucleus (Yeterian and Van Hoesen, 1978; Selemon and Goldman-Rakic, 1985). As Selemon and Goldman-Rakic (1985) have demonstrated, that cortical areas project to the same striatal district does not guarantee that their fibers will intermix, as opposed to interdigitate (see also Yeterian and Van Hoesen, 1978). Their most striking counterexamples are terminals from either the superior temporal gyrus or orbitofrontal cortex interdigitating with terminals from dorsolateral and dorsomedial prefrontal cortex (see their figures 11 and 14). Our analysis in the cat, which indicates that cingulate and dorsalmost prefrontal cortices connect with matrix tissue in central caudate nucleus while ventral prefrontal and rostral temporal projections reaching this same district innervate striosomal tissue, suggests that the interdigitation observed by Selemon and Goldman-Rakic is due to a segregation of afferent terminals along histocompartmental lines. Moreover, it predicts compartmental convergence between properly chosen afferent sources, such as those from rostral temporal and ventromedial prefrontal cortex. Obviously, the arrangements for cortical regions

[12]Yeterian and Van Hoesen (1978) pointed out that the converse proposition- that if corticostriatal projections exhibit overlap, then the cortical areas in question are connected- also appears to hold. In fact, the evidence in our material for this principle is even more secure.

that show a dual pattern of compartmental innervation will be more complex, but our findings should correctly predict whether overlapping striatal inputs from well-separated cortical areas intermix or interdigitate.

Published chartings of corticostriatal projections in the monkey offer some guide to primate correspondents for the distinctions among cortical areas that we have drawn in the cat. From the report of Van Hoesen et al. (1981), it appears that areas TG of the temporal pole and TA of the superior temporal gyrus, in projecting to ventral and medial caudate nucleus, may be equivalent to the striosomally targeted rostral temporal cortex of the cat. Once allowance is made for the temporal rotation of connectionally defined striatal districts in the monkey, the striatal projections from the monkey visual areas TE and TF appear strikingly similar to that of visual area PS and nearby rhinal cortex in the cat. This suggests that homologues of cat caudal temporal cortex may occur in caudal parts of monkey temporal cortex.

Most corticostriatal projections in the cat are extended in the dorsoventral dimension and organized in the mediolateral dimension

That corticostriatal projections from association cortex are extended along the dorsoventral axis was recognized in tracing studies based on axonal degeneration (Carman et al., 1963; Webster, 1965; Kemp and Powell, 1970) and has been confirmed for the monkey by modern anatomical techniques (Yeterian and Van Hoesen, 1978; Selemon and Goldman-Rakic, 1985). We have observed, with the autoradiographic method, a similar arrangement in cat. Dorsoventrally extended terminal fields predict a mediolateral organization to the arrangement of inputs from different cortical areas. The issues are, then, what controls the mediolateral disposition of a corticostriatal projection?; and do corticostriatal projections form largely separate projection domains in striatum, or is partial terminal-field overlap common?

Selemon and Goldman-Rakic (1985) have concluded that, in monkey, corticostriatal projections typically interdigitate or segregate along the mediolateral axis, suggesting the presence of functionally distinct domains. In our material, we were struck by the tendency of labelled projections (1) to travel through the central core of the caudate nucleus, from the ventricle dorsomedially to the vicinity of the internal capsule ventrally (see Fig. 6-16); or (2) to accumulate along the bottom three-fourth's of the ventricular face and stretch into adjoining ventral caudate nucleus (see Fig. 6-2B); or (3) to terminate in lateral caudate nucleus and putamen. Moreover, the suggested mixing of corticostriatal projections that share the same sector of termination, such as in dorsolateral caudate nucleus among anterior parietal and sensory motor connections, made sense functionally. However, there was no compelling evidence for internal striatal boundaries that were strictly observed by corticostriatal innervations. For example, rostrocaudal shifts in tracer-deposit position in parietal and posterior cingulate cortex produced apparently graded mediolateral shifts in striatal terminal field position. Moreover, most of the striatal projection-patterns we saw, although densest in one of the three mediolateral zones noted above, freely extended into the others. This was particularly true of projections to ventral caudate nucleus (*e.g.*, see Fig. 6-12C). Finally, certain deposits, such as those in area 6aβ of the anterior sigmoid gyrus, clearly label projections that cut across two domains- in this example, between dorsomedial and dorsolateral sectors of the caudate nucleus. There are sets of injections that, when compared, would suggest separate mediolateral functional domains in striatum (for example, sensory motor and posterior parietal deposits see Fig. (A/HRP)). But, at least from the evidence of our material, a conclusion of non-overlapping domains is premature.

One feature of this mediolateral organization was strikingly clear, though.

Projections from early sensory areas and primary motor cortex terminated in lateralmost caudate nucleus and putamen, and, for the olfactory system, in lateral olfactory tubercle. Fibers from late sensory districts and higher-order association cortex occupied an intermediate striatal territory. Neocortex reaching the most medial caudate nucleus- rostral cingulate, ventral prefrontal and ventral temporal cortices- is that found at the end of the chain of cortical areas leading to limbic system. Finally, the most medial striatal district, medial nucleus accumbens, is known to receive direct cortical input from the hippocampal formation (Fox, 1943; Carman et al., 1963; Raisman et al., 1966; Groenewegen et al., 1982; Kelley and Domesick, 1982). The mediolateral placement of corticostriatal projections appears to be neither arbitrary nor particularly decided by a simple global topography. The best predictor of the mediolateral termination of a corticostriatal projections would seem to be the distance of that cortical area along the transcortical march into limbic system (Jones and Powell, 1970; Barbas, 1986).

Evidence for a dual pattern of compartmental innervation by single areas of cortex

A constant feature of our cases with deposits in prefrontal and insular cortex was a striatal innervation-pattern in which striosomes are filled dorsally and avoided ventrally in the field of termination. This pattern was present in nearly every case, whatever the size and position of the injection site or the length of the post-operative survival time. The only experiments in which we did not see a dorsal fill-ventral avoid pattern were a spatially restricted set of deposits that elicited filling of striosomes to the base of the caudate nucleus. As we will argue below, these cases were not departures from the dorsal fill-ventral avoid pattern, but instances of a more general version of it.

The constancy of the dorsal fill-ventral avoid pattern across our prefrontal

cases does not guarantee that a single cortical area can give rise to a bicompartmental innervation of striatum. This proposition has in fact proved difficult to test directly. The difficulty is more fundamental than the technical requirement that cortical deposits be large enough to produce striatal labelling that can be compared with the histochemistry: there are no "areas" in prefrontal cortex that have reliably identifiable borders that have been defined more than one way- for example, by cytoarchitectural and connectional criteria (Cavada and Reinoso-Suarez, 1985). Consequently, no cortical deposit, wherever placed and however small, could establish that single areas have multiple innervation-patterns.

However, the indirect evidence accumulated in this study strongly supports the view that some cortical areas have dual patterns of compartmental termination. This is best seen by considering the difficulties posed by our findings for the competing analysis of our case-material, that all cortical areas have single patterns of compartmental innervation. This alternative analysis must hold that *every* deposit that elicited a multiple innervation-pattern (cf. Figs. 6-5, 6-10 and 6-11) must have crossed a border between a cortical area that fills striosomes and one that avoids them. It would appear, in this analysis, to be very difficult to avoid straddling such borders, because they need to have been implicated in each of our small deposits in prefrontal cortex (Fig. 6-7, and because the absence of projections that either filled striosomes dorsally (alone) or avoided them ventrally (alone) would mean that we were unable in any case to restrict a deposit to just one area. It would seem that either these compartmentally distinguished cortical areas are very small and well-interdigitated, or they are bizarrely shaped, with extensive and irregularly contoured borders.

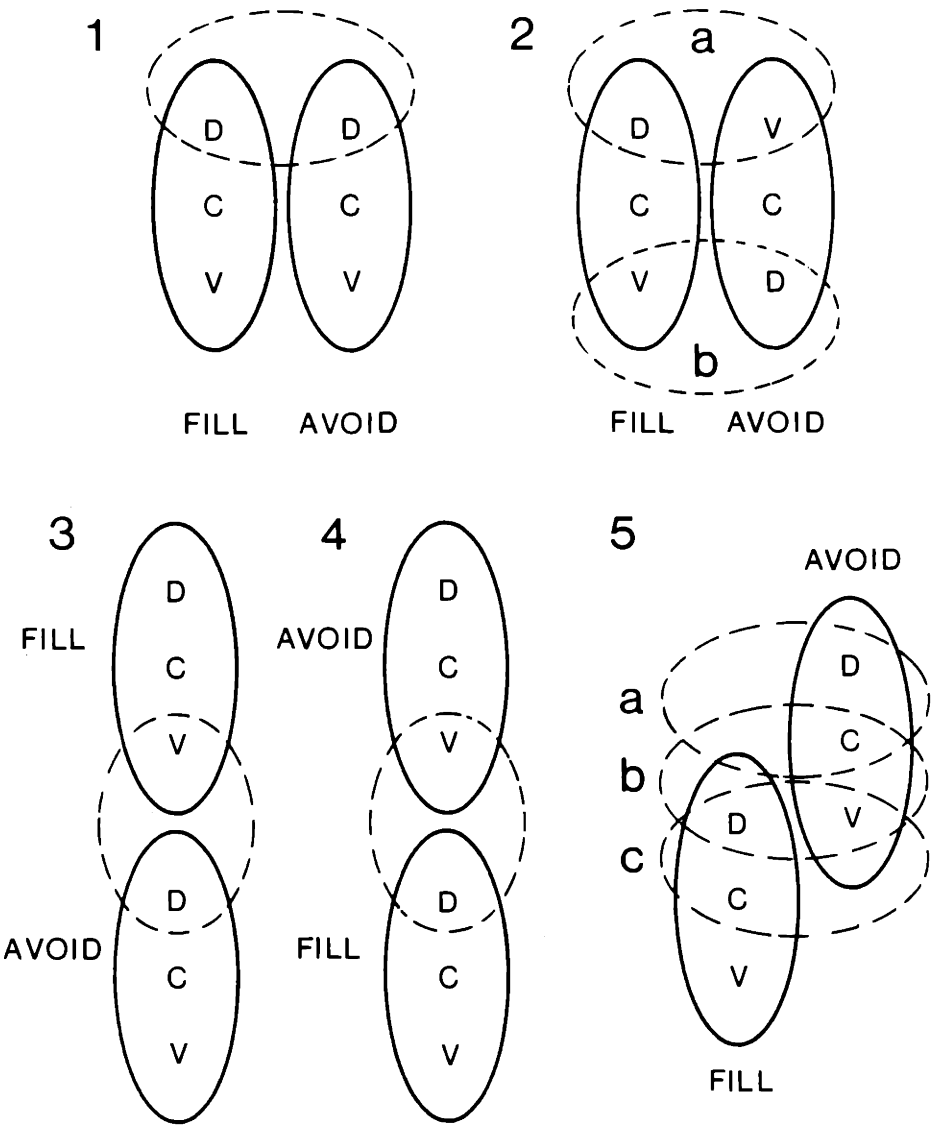
Additional difficulties for a scheme of single compartmental targets for all cortical areas are presented by the structure we have seen in the bicompartmental

innervation-pattern: it is always organized as dorsal fills and ventral avoids, and the elevation of the dorsal fill-ventral avoid transition shifts with injection site position. A natural approach in accounting for this kind of spatial organization is to postulate that areas with single compartmental targets have topographically organized projections to striatum. The spatially specified, dual compartmental innervation-pattern would then arise from tracer-deposits involving adjoining cortical areas, each with its specified compartmental destination and its own corticostriatal topography. Figure 6-15 was prepared to illustrate the topological constraints that such a scheme must observe.

In Panel 1 of Figure 6-15, two adjoining cortical areas, one of which fills striosomes, the other of which avoids them, are represented by heavily outlined ovals. The topographical organization of the striatal connections of these areas is indicated by D-C-V, which are interpreted as sector D projects to dorsal caudate nucleus, and sectors C and V reach central and ventral caudate nucleus, respectively. The dotted outline represents a tracer-deposit into cortex and suggests the kinds of innervation-patterns to which that cortical architecture might give rise. In the example of the deposit outlined in Panel 1, both compartments would be labelled in the dorsal caudate nucleus. Consequently, adjoining cortical areas with distinct compartmental targets can not be in topographic register as this would not allow distinct and spatially separate compartmental innervations.

The arrangement in Panel 2 suggests the implications of adjoining cortical fields with inverted topographic maps. A deposit such as **a** would elicit the expected dorsal fill-ventral avoid pattern. This architecture would, though, also allow for Deposit **b**, from which striosomes in the caudate nucleus would be filled ventrally but avoided dorsally. This is a pattern that was never seen in the case-material. If, then, topographically organized, compartmentally specified cortical

Figure 6-15: Diagrammatic illustration of the topological constraints imposed on cortical architecture were corticostriatal projections to be restricted to a single pattern of compartmental termination. See text for description.


1
D
C
V
D
C
V
FILL
AVOID
2
a
D
C
V
V
C
D
b
FILL
AVOID
3
FILL
D
C
V
AVOID
D
C
V
4
AVOID
D
C
V
FILL
D
C
V
5
AVOID
a
b
c
D
C
V
D
C
V
FILL

areas are to adjoin one another, it can only be along restricted zones. As Panels 3 and 4 demonstrate, this contact must be limited to the ventrally projecting sector of 'avoid' cortex and the dorsally projecting sector of 'fill' cortex (as in Panel 4).

The scheme presented in Panel 4 is inadequate in accounting for our experimental observations because it does not provide for movement in the elevation of the dorsal fill-ventral avoid transition with movement of injection site position. The partially shifted arrangement described in Panel 5 is successful in this regard: Deposit **b** would produce striosome fills in dorsal caudate nucleus and avoids in central and ventral caudate nucleus, whereas Deposit **c** would fill striosomes in dorsal *and central* caudate nucleus and innervate matrix tissue in ventral caudate nucleus.

The success of the scheme in Panel 5 in describing certain corticostriatal relationships does not inexorably lead to the conclusion that it is a correct model of prefrontal cortical organization. In fact, we view it as a pictorial description of the general form of corticostriatal projection-patterns[13]. Moreover, even with the scheme in Panel 5, to account for the data we have collected, borders between 'fill' and 'avoid' cortex still must pass through nearly all of our prefrontal and insular injection sites. There is precedent from physiological mapping studies of cat visual cortex for single cortical areas that are stretched, almost deformed, by the requirements of cortical architecture, and that still maintain their identity and topographic organization. It does not seem possible, though, that the frontostriatal projection-pattern can be accounted for by one 'fill' area and one 'avoid' area, however convoluted their juxtapositions.

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[13]Note, for example, that **a**- that is, avoids in dorsal and central caudate nucleus- is an allowed corticostriatal projection-pattern, but that it is observed by parietal and cingulate cortex and not by prefrontal cortex.

More generally, there is no good reason to reject the possibility that individual cortical areas might vary their compartmental targets according to striatal sector innervated. Analogous arrangements are well-known from thalamocortical anatomy. A tracer-deposit placed in the paralaminar nuclei of the thalamus will produce labelling in cortex that switches between two patterns of lamination, according to the cortical area innervated (Herkenham, 1980; Berson, 1980). There is no evidence- and, in fact, the objection has not even come up in the literature- that these observations of multiple lamination-patterns are a result of injection site involvement of cryptic thalamic nuclear compartments.

Individual cortical areas also engage in multiple lamination-patterns in their transcortical association connections (Rockland and Pandya, 1979; Maunsell and Van Essen, 1983). In fact, in an arrangement reminiscent of the corticostriatal projection, the groupings of cortical areas that receive the different patterns of laminar innervation change with cortical area injected. Interestingly, retrograde tracing experiments indicate that, within a cortical area, neurons in different layers project to different cortical areas and, therefore, give rise to the different lamination patterns (Rockland and Pandya, 1979; Maunsell and Van Essen, 1983). Similarly, there is some evidence that, within a thalamic nucleus, distinct thalamocortical neurons project to different cortical layers (Diamond, 1983). Corticostriatal projections are known to issue from more than one cell type and more than one layer of cortex (Kitai et al., 1976b; Oka, 1980; Royce, 1982; Tanaka, 1987). It seems possible, then, that while individual cortical areas may project to both striatal compartments, the destination of individual corticostriatal neurons within a cortical area may be compartmentally designated.

To recapitulate: we have not conclusively demonstrated that single areas of cortex can participate in a dual pattern of compartmental affiliation. Our findings,

though, strongly support this analysis. The alternative view would require a mosaic architecture for frontal and insular cortex of great complexity, one probably constructed of multiple areas whose relative positions are constrained along the lines shown in Panel 5 of Figure 6-15. Moreover, the size of these areas would severely test our notion of what a cortical area is. And, it would remain the case that deposits in fairly restricted regions of cortex elicit a dorsal fill-ventral avoid pattern of innervation. We will argue the remainder of the discussion as if single cortical areas do change their compartmental target according to their striatal sector of termination. The conclusions that follow could, if necessary, be fully restated in terms of "restricted, local regions of cortex"

Ordering of cortical areas based on the topographical and compartmental organization of their connections with striatum

Strictly speaking, if all striatal afferent connections restrict their distributions to one histochemical compartment or the other, there is no direct way, based on inputs, to relate striosomes and matrix. Consider the thalamostriatal connection. Our analysis suggests that this system is composed of two divisions, medial and lateral, distinguished because they send their fibers to striosomes and matrix, respectively (see chapter 5). Since we already know that the histochemical compartments are separate entities, a finding that they have separate inputs does not suggest anything new about the relationship between striosomes and matrix. What is called for, instead, is an examination of aspects of these thalamostriatal divisions other than their striatal targets. An example of this indirect analysis would be comparison of the afferent or non-striatal efferent connections of the medial and lateral thalamostriatal systems.

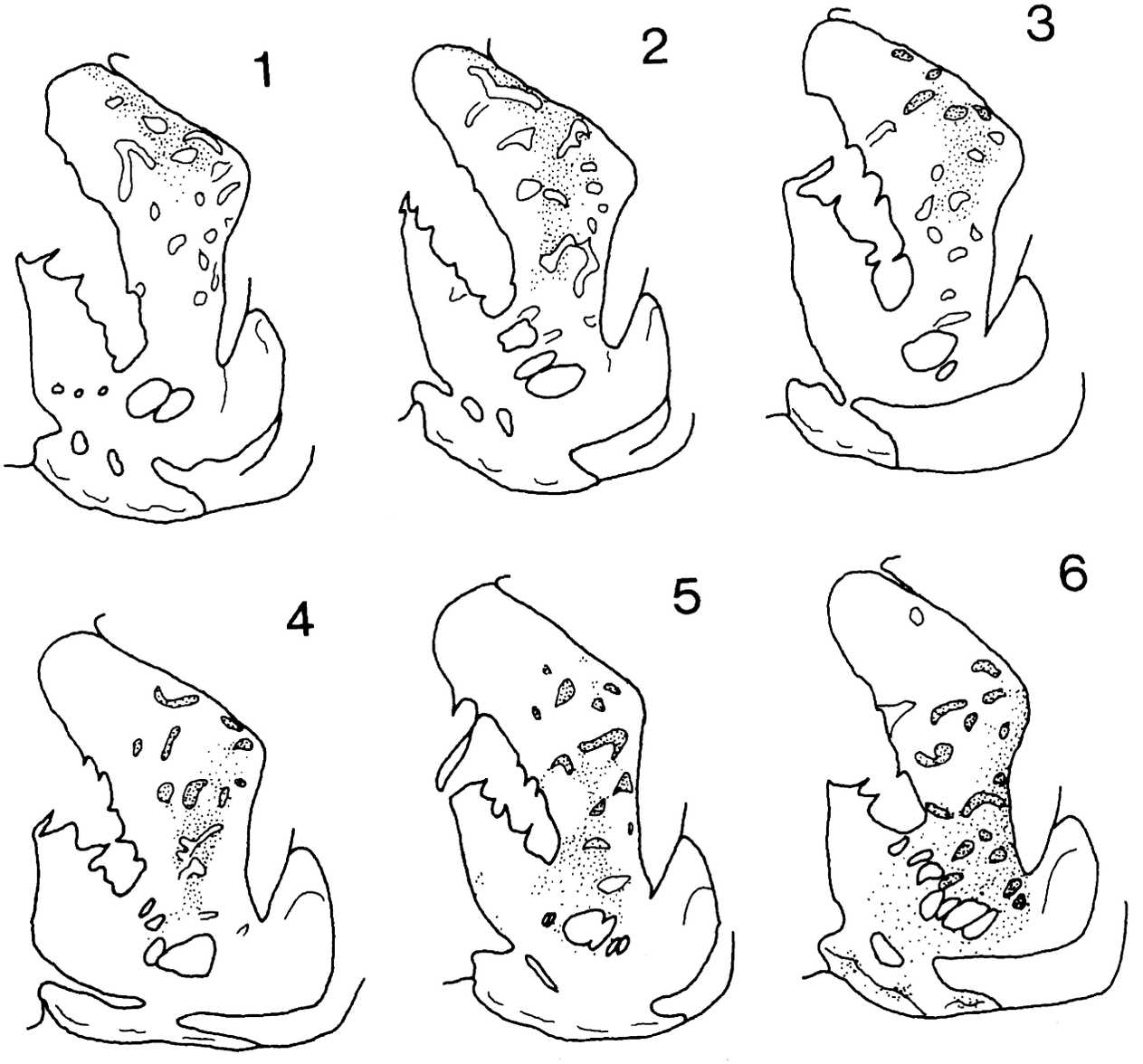
By contrast, the finding that cortical areas do not restrict their projections to one of the striatal compartments allows us to relate striosomes and matrix directly,

in terms of the pattern of their joint afferentation. The observation that this dual innervation is spatially organized- regions of cortex innervate one compartment in part of their striatal field of termination, and the other compartment elsewhere- means that our description of the relationship between striosomes and matrix will be in spatial terms, relating striosomes in one part of the striatum to matrix tissue somewhere else. Because the dual innervation is constrained spatially to a dorsal fill-ventral avoid pattern, we are assured that this relationship between striosomes and matrix will be consistent across cortical areas.

The dorsal fill-ventral avoid constraint has a deeper implication for the nature of the relationship between striosomes and matrix. This is seen by analysis of the character of the constraint. First, it is organized along a single dimension, roughly the dorsoventral axis. Second, it is polarized (fills are always dorsal). Third, it is not fixed along the dorsoventral dimension (this is because transitions between dorsal fills and ventral avoids have been observed at more than one dorsoventral elevation). These three properties, one-dimensionality, polarity, and multiple values, are sufficient to interpret the dorsal fill-ventral avoid constraint as an ordering constraint. Because this interpretation is seen most easily by an examination of corticostriatal projection-patterns, we will describe first a novel ordering of cortical areas that the dorsal fill-ventral avoid pattern implies. We will then show how this ordering of cortical areas provides an economical (and formal) description of the relationship between the input to striosomes and the input to matrix.

Figure 6-16 offers a graphic demonstration of the ordering of cortical areas based on their pattern of striatal innervation. The sections illustrated in Panels 3, 4 and 5 exhibit a dorsal fill-ventral avoid pattern of fiber-labelling. The elevation of the compartmental switch is different across the sections and they are ranked, by

Figure 6-16: Chartings of corticostriatal fibers in relation to AChE-poor striosomes in six autoradiographic cases. Sections at comparable anteroposterior longitudes were chosen for illustration. The cases are ordered according to the range of their labelled fibers within the caudate nucleus and the elevation at which the compartmental innervation switches from striosomal to matrical. This ordering of striatal labelling-patterns implies an ordering across the cortical areas injected in these cases. (1) Posterior parietal cortex (case CRCx-8); (2) Anterior cingular area (case CHRC-3); (3) Dorsomedial prefrontal cortex (case CRCx-35); (4) Dorsal proreal cortex (case CHRC-9r); (5) Insular cortex (case CRCx-24); (6) Rostral temporal cortex (case CRCT-2L).


1
2
3
4
5
6

convention, with more ventral transition taking higher ordinal values. The nature of the dorsal fill-ventral avoid constraint is that it restricts the possible patterns of bicompartmental innervations, but it does not require that all innervations be multiple. Single compartmental innervations are allowed, and they are construed as dorsal fill-ventral avoid patterns where the transition occurs virtually, at the limits of dorsal striatal tissue. The transition in 'avoid only' innervations would sit at the dorsal boundary of the striatum, so these patterns are ranked lowest. By similar arrangements, 'fill only' patterns are ranked highest (see Panels 1 and 6 of Fig. 6-16).

Two technical points about this ordering are of interest. First, the dorsal fill-ventral avoid constraint does not establish an ordering between projection-patterns that share the same transition-elevation, but differ in the range of the striatal tissue innervated. Panels 1 and 2 offer an example of such patterns: both illustrate terminations in dorsal caudate nucleus that avoid striosomes, but the labelling in Panel 2 extends much further ventrally. A natural stipulation in such cases, one in line with the dorsoventral organization of the constraint, is to place the patterns that extend further ventrally higher in the ordering, as we have done in Panels 1 and 2 in Figure 6-16. A second point of interest concerns our failure to observe 'dorsal fill only' and 'ventral avoid only' patterns in our case-material. This observation could be captured by a strengthening of the dorsal fill-ventral avoid constraint to include a requirement that striatal labelling be realized through the sector of the dorsal fill-ventral avoid transition. This would mean that all 'avoid only' patterns must include labelling in the dorsal caudate nucleus, and that all 'fill only' patterns include labelling to the base of the caudate nucleus and into the nucleus accumbens (as we have found).

Panel 5 of Fig. 6-15 offers a pictorial exposition of one general form of the

dorsal fill-ventral avoid constraint that predicts both the covert ordering of the projection-patterns and the technical points just noted. In this model, the broken-lined ovals are interpreted as outlining the features present in possible corticostriatal projections. As illustrated, many patterns, including dorsal fill-ventral avoids (**b**,**c**) and dorsal avoids fills only (**a**, are produced, but certain configurations, such as dorsal fills only, are excluded. The top-to-bottom position of the horizontal ovals in the figure corresponds to the relative ordering (low-to-high) we have suggested for the projection-patterns. Note, also, that projections that avoid just in the dorsal caudate nucleus will be ranked lower than those that avoid in both dorsal and central caudate nucleus (as we stipulated in Fig. 6-16). This particular model of the dorsal fill-ventral avoid constraint does not, however, generate for all known patterns of corticostriatal compartmental innervation: in particular, a matrix innervation that covers the full dorsoventral extent of the striatum (such as that from area 24 of the medial limbic cortex) is not available.

An ordering of corticostriatal projection-patterns directly implies an ordering of the cortical areas that produce these patterns. One ordered set of cortical areas, constructed by reading off the Panels in Figure 6-16[14], is <posterior parietal, cingular, dorsomedial prefrontal, ventrolateral prefrontal, insular, rostral temporal> cortex. The leftmost structure, posterior parietal cortex, is ranked lowest, in accord with the rank of its projection-pattern, the rightmost element is ranked highest, and the intervening elements take on intermediate values[15]. This set is not fixed. For example, caudal ventromedial prefrontal cortex is equivalent in

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[14]See also Table on page 268.

[15]As before, the choice of which extreme is 'higher' in the ordering is by convention. The choice we made, that the 'fill only' pattern is highest, was informed by our suspicions about the relative functional roles of striosomes and matrix (see below). But, if the language of ordering had provided us with neutral terms, we would have used them.

this ordering to rostral temporal cortex, and could substitute for it as the highest-ranked element in the set. As additional detailed information about corticostriatal projections becomes available, the ordering can be expanded.

At least in prefrontal cortex, the ordering of cortical zones according to their dorsal fill-ventral avoid pattern of corticostriatal projection appears to correspond closely to their dorsoventral position in cortex (highest ranked cortex is ventralmost). The observation that, across the pseudosylvian sulcus, the higher ranked temporal cortex is ventral to insular and post-insular cortex (*e.g.*, compare cases CRCT-2L and CRCx-32R), suggests that there may be some principle at work here. One possibility, raised by our suggestion that cortex projecting homogeneously to matrix forms a single plate, is that cortical areas that share the same position in the dorsal fill-ventral avoid ordering form a single cortical expanse, that these cortical expanses run as bands parallel to the frontal and lateral margin of the hemisphere, and that the bands are arrayed in accord with their position in the dorsal fill-ventral avoid ordering, with those bands ranked highest lying nearest the lateral margin formed by primary and secondary olfactory cortices. There is an obvious test of this speculation. Rostral temporal cortex and caudal ventromedial prefrontal cortex share the same ranking. If a band of similarly ranked cortex connects them, it must run lateral to the granular insular cortex we have studied, in the depths of the rhinal sulcus. The prediction for future studies of the corticostriatal projection to test, is that deposits placed in dysgranular or dorsal agranular insular cortex would preferentially label striosomes in the base of the caudate nucleus.

The ordering constraint operates in the dorsoventral axis. Consequently, to the extent there are separate mediolateral domains in the striatum, there will be separate orderings of cortical areas. The example we offer in Figure 6-16 involves

cortical projections directed to the central portion of the caudate nucleus, but, at least for medial caudate nucleus, a comparable ordering can be constructed from the evidence of our experiments: <'prelimbic', rostral ventromedial prefrontal (cf. CRCx-6), caudal ventromedial prefrontal> cortex. The lateral striatum is more difficult. Situated leftmost in such an ordering would be anterior parietal cortex. Lateral praesylvian cortex, which fills dorsally and avoids ventrally in lateral striatum, would be ranked next. We have not identified a cortical zone that is directed to ventrolateral striatum and fills striosomes there, although many striosomes in this region were labelled in our ventromedial prefrontal and rostral temporal cases. The position of motor cortex is also unclear (see above); the possibility that a motor-premotor zone reaches both compartments, while the SMA is restricted to the matrix, is of particular interest as it would suggest (1) an ordering distinction among motor and premotor areas and (2) a placement of the SMA with parietal cortex at the extreme of such an ordering. In short, the organization of cortical projections to lateral striatum requires further study.

As a general point, it is not guaranteed that all sectors of striatum (and, by extension, their afferent cortical areas) can be involved in some ordering of corticostriatal projection-patterns. The sensory cortex-recipient zones of caudolateral striatum are good candidates for such sectors since we have not identified cortical zones that fill striosomes there, much less ones that engage in a dual innervation-pattern. Given that the sensory motor-recipient district might, finally, prove intractable to this kind of analysis, it seems possible that this compartmental ordering could be restricted to association cortex and its striatal targets. There is no reason, though, why many of the parasensory areas of the heterogeneous matrix-projecting cortex can not be incorporated in this scheme as they either restrict their projections to the matrix, or, if they invade striosomes, do so in the dorsal caudate nucleus.

The ordering of cortical areas is a major theme of cortical anatomical investigations over the last twenty years (Jones and Powell, 1970; Rockland and Pandya, 1979; Maunsell and Van Essen, 1983; Barbas, 1986). The findings of these studies concerned the progression of connections leading from sensory and motor cortices to association cortex and into the limbic system. Our findings, although engaging these progressions in part, at least in the frontal cortex, mainly point to an orthogonal ordering scheme, one that places rostral temporal and parietal cortex not at their respective ends of pathways leading away from sensory cortex, but at the opposite ends of an ordering of association cortices. That these cortical areas at the extremes of this ordering differ, is well-known; we implicitly reviewed these differences in our discussion of the distinctions between cortex that is restricted to matrix tissue and cortex that innervates striosomes. What is novel in our analysis is the ability to order nearly all the areas of association cortex.

Our ordering of cortical areas is based on corticostriatal connections, so there is no requirement that it mirror any sequence of cortical areas established by transcortical connections. It appears, though, that portions of this corticostriatal ordering have been observed by Barbas (1986) in retrograde tracing studies of monkey cortex. She examined the variation across cortical areas of the ratio of infragranular to supragranular neurons that contribute projections to identified regions of prefrontal cortex. Quantitative analysis suggested several collections of adjoining cortical areas that could be ordered according to the value of the ratio. Most of these orderings, for example, one leading from occipital into temporal cortex, recapitulated progressions known from the studies of Jones and Powell (1970), and Pandya and Van Essen and their colleagues (Rockland and Pandya, 1979; Pandya and Seltzer, 1982; Maunsell and Van Essen, 1983; Van Essen, 1985) . However, two were restricted to frontal cortex and ran from the dorsolateral

frontal cortex laterally to orbital cortex, and medially to ventral prefrontal cortex. These progressions, then, are very similar to orderings we would apply to homologous cortex in the cat (see also Musil and Olson, 1986). Our ordering scheme, though, is not limited to one cortical lobe, but includes frontal, insular, temporal, cingulate and parietal cortices.

We considered earlier whether the thalamic and amygdalar connections of a cortical zone would predict its access to the striosomal compartment. For the thalamus, we found that, given weak or no anterior nuclear connections, the presence of more medial thalamic labelling roughly correlated with, first, the presence of striosomal labelling and, second, more ventral access to the striosome compartment. Thus, cortical areas higher in the ordering project more medially in the medial, ventral and lateral nuclei of the dorsal thalamus. Kievet and Kuypers (1977), in distinguishing regions of frontal cortex according to the mediolateral placement of their thalamic labelling, suggested that the primary organizational principle of thalamocortical connectivity is not based on specific thalamic nuclei projecting to specific cortical areas, but rather one of global topography. Our finding that position of cortical areas in the striosomally based cortical ordering correlates with the mediolateral locus of their thalamic labelling suggests that the mediolateral organization of thalamus may reflect not simple topographic placement, but the operation of deeper, highly specific principles of forebrain connectional organization. Support for this possibility comes from our observations on the thalamostriatal connection- thalamic projections to striosomes arise from the midline; that to matrix issues from more lateral structures (see Chapter 5).

For the cortical areas we studied, we were unable to show a tight relationship between access to striosomes and projections to the basolateral complex of the amygdala. The striosomally based cortical ordering does, however, suggest a

privileged position for the basolateral nucleus of the amygdala. Its striatal projection-pattern would be ordered highest, were it a cortical area. Moreover, the thalamoamygdalar connection is also organized mediolaterally: midline thalamus projects to the basolateral nucleus; paramidline structures, to the lateral and basomedial nucleus. It would appear, then, that affiliations with striosomes control the mediolateral placements of the three thalamic efferent circuits to striatum: the direct thalamostriatal projection, and the indirect thalamoamygdalostriatal and thalamocorticostriatal connections.

A connectional analysis of the relationship between striosomes and matrix

There are no long-distance association connections in striatum. The finding that striatal afferent connections are extended in the dorsoventral dimension suggests a linkage, by joint afferentation, of striatal tissue separated along the dorsoventral axis. Our observations indicate that this linkage is also compartmentally specified- striosomes share input with subjacently located matrix tissue. The insights that the dorsal fill-ventral avoid constraint gives us about the relationship between striosomes and matrix depends on the spatial organization of striatum; therefore, the dorsoventral position, as well as the character of adjoining striatal sectors, can be no more arbitrary than the relationship between striosomes and matrix. This implies that dorsoventrally contiguous striatal sectors are also ordered. Like the striosomally based ordering of cortical areas, this ordering of striatal sectors is not based on association connections; but it is realized physically, in the dorsoventral position of a striatal sector.

This ordering of striatal sectors can be extended into at least part of the ventral striatum. Corticostriatal connections from certain areas of cortex, such as the anterior limbic area or ventral prefrontal cortex, extend without interruption

Ordering of Cortical Areas according to their Striosomal Affiliations

	Parietal	Dorsomedial Prefrontal	Ventrolateral Prefrontal	Insula	Temporal
DORSAL CN	avoids	fills			
CENTRAL CN		avoids	fills	fills	
VENTRAL CN			avoids	fills	fills
BASAL CN				avoids	fills
NUCLEUS ACCUMBENS					labels

from the caudate nucleus into the nucleus accumbens. As the nucleus accumbens is striatal tissue, it would seem that we should be able to incorporate this extension of the projection into any general account of corticostriatal connections; and, specifically, that we can apply the dorsal fill-ventral avoid constraint to these projections. This is successful- that is, without violations of the constraint- provided we construe nucleus accumbens labelling as labelling of the matrix compartment. This may seem counterintuitive- the fact that both striosomes and nucleus accumbens are innervated by the medial thalamostriatal projection system, for example, would appear to suggest that nucleus accumbens tissue is like striosomal tissue. The insight, however, of the dorsal fill-ventral avoid constraint is that matrix tissue ventral to a given striosome is also, by the criterion of shared input, 'like' that striosome. If we apply the dorsal fill-ventral avoid constraint to corticostriatal projections that extend into the nucleus accumbens, and interpret the nucleus accumbens as striosomal tissue, we discover violations. An example is the projection of the anterior limbic area, which projects to dorsal striatal matrix and the nucleus accumbens. This would be a (disallowed) dorsal avoid-ventral fill pattern. A given striosome, then, is similar to ventral striatal tissue in the same way it is similar to ventrally adjoining matrix tissue. The feature which sets ventral striatum apart is its ventralmost position in a dorsoventral ordering of striatal sectors.

The example just reviewed may give the impression that the dorsal fill-ventral avoid constraint does not particularly "constrain" the relationship between striosomes and matrix if a given striosome is affiliated with both matrix and striosomes ventral to it and (presumably) striosomes dorsal to it. However, for the relationship between striosomes and matrix within a given region of striatum, the dorsal fill-ventral avoid constraint on cortical input allows for a powerful and

economical description of the difference between the inputs to striosomes and matrix. This is illustrated by the Table. We have there entered in tabular form the example of the ordering of cortical areas illustrated in Figure 6-16. The columns represent the compartmental innervation-patterns of the cortical areas, which are listed left-to-right according to their position in the ordering. The rows indicate the compartmental patterns of innervation for the designated cortical areas for that sector of striatum. The relationship between the inputs to the two compartments is clear: input to striosomes arises from cortex that is higher in the ordering.

This, then, is a general description of the relationship between the two compartments in terms of their afferent connections from cortex. The input to any striosome is distinguished from that to adjoining matrix tissue in being further along the continuum represented by the corticostriatal ordering of cortical areas. Clearly, the task of understanding this relationship functionally can best proceed by inquiry into what variable determines a cortical area's position in this ordering. An important clue here may come from study of the functions of the basolateral nucleus of the amygdala, as its pattern of striatal input would place it at one extreme of the ordering (see Chapter 4).

This connectional analysis of the relationship between striosomes and matrix suggests an analogy at a fairly deep level to the anatomy of cortex. Consider the relationship of layer 4 within cortex in the context of transcortical connections at early stages of sensory processing (Rockland and Pandya, 1979; Maunsell and Van Essen, 1983). Like layer 4, striosomes occupy on the order of 15% of the tissue in which it lies (Bonin, 1950). Like layer 4 across several cortical areas, striosomes across several sectors of striatum do not receive identical input. Like layer 4 in its relationship to the other layers and to nearby cortex, the relationship between striosomes and matrix is constant when defined in terms of adjoining sectors of

striatal tissue. To be crude but explicit: layer 4 in a give cortical area is 'closer' to cortex that is lower in the hierarchy of cortical areas it is to areas that are higher. Striosomes are 'closer' to striatum that is ventral to it than to striatum that is dorsal to it.

There are contrasts in this analogy. Most notable is that the information delivered to layer 4 is usually quite close, in terms of processing, to the delivered to adjacent layers, whereas the inputs to striosomes can be quite distant from that present in adjoining matrix, where distance is measured not only by physical distance across cortex, but by connectional and, probably, functional criteria. Perhaps this is why there is no call for association connections within striatum.

Functional implications

The striosomal-based ordering of cortical areas is not dependent on transcortical association connections. It is not dependent on concatenated, association connections of any kind. It is a covert ordering. As such, it is not straightforward to apply the type of functional interpretation normally applied to 'ordered' brain structures- in the example of transcortical connections, this interpretation might be as chain of areas involved in successively more complex and abstract aspects of sensory processing. There are hints, however, for a functional interpretation of the ordering. The hints are (1) that the striatal system is deeply involved in motor function, and (2) that the relationship between striosomes and matrix in a given striatal region is a reflection of the relationship between striatal regions.

One approach, then, to the question of the relationship between striosomes and matrix is to examine what functions have been attributed to different sectors of the striatum. Rosvold and his colleagues have carried out an extensive series of neuropsychological experiments in monkeys on the functions of frontal cortex and

caudate nucleus (reviewed in Chapter 1). Rosvold (1968) has summarized his behavioral findings as follows: "The frontal cortex and the head of the caudate nucleus have similar functions. These functions appear to be involved principally with the modulation of activity in the motor system which is necessary for an animal to accurately direct his behavior. At least two such functions are dissociable, each related to a different cortical-subcortical system. The orbital frontal cortex and ventrolateral sector of the caudate appear to determine whether or not a response will occur, while the lateral frontal cortex and anterodorsal sector of the head of the caudate determine where it will occur." As we noted, Johnson and Rosvold (1968,1971) suggested that these corticostriatal systems are brought together at subsequent stages of basal ganglia processing, while others have suggested that the paths are kept separate until they return to cortex (Alexander et al., 1986).

Our anatomical analysis suggests, instead, that cortical inputs that reach a given dorsoventral domain of the striatum will be brought together, if not by direct overlap, then by compartmentally specified, pair-wise interdigitation of ordered cortical areas. Such an analysis does not contradict the behavioral findings of Rosvold and coworkers; recall that they were not successful in either dissociating caudate nucleus function from that of frontal cortex, or in producing deficits from striatal lesions that were as severe as those from cortical lesions. This is consistent with the view that their behavioral tasks did not test striatal dysfunction specifically.

When our anatomical analysis of the difference between striosomes and matrix is applied to the behavioral account of Rosvold of the principal functions of the different striatal sectors, a provocative possibility emerges. This is that, for

striatal tissue bridging Rosvold's 'sectors' of the caudate nucleus[16], striosomes will, in virtue of their cortical input from ventral prefrontal cortex, be concerned with whether a behavioral response will occur; the matrix will participate in circuitries (from dorsal prefrontal cortex) more concerned with "where it will occur". Although this speculation is specific for one striatal district, it does suggest a functional interpretation of the corticostriatal ordering of cortical areas that we have described, one that would suggest why the striatal system seems so uniquely linked to motor system control: it is that these cortical areas are ordered according to the stage of the motor planning process to which they contribute, where stages run from deciding to make a behavioral response to directing where it is to occur. The striosome-matrix interaction would then be one way by which these stages are integrated.

In a somewhat more concrete vein, our findings have specific, though rather indirect, predictions for what basal ganglia researchers might look for in searching for neurophysiological differences between striosomes and matrix tissue. The observation that striosomes in one striatal region share input with matrix in more ventral districts of striatum, coupled with the physical predominance of matrix over striosomal tissue, suggests that if a behavioral task is successful in activating a large percentage of the neurons in a given striatal region, then it might be successful in differentially activating striosomes in a more dorsal striatal district. Rolls and colleagues (1983, 1984) have found that many units in the head of the caudate nucleus whose activity level is "related to the preparation for and initiation of behavioral responses in response to environmental cues" (Rolls et al., 1984). By contrast, these kinds of units were "relatively rare (10%) in the

[16]See, for example, the central caudate nucleus entry in the Table.

putamen"[17]. Most neurons in the putamen showed, as expected, unconditional phasic activity in association with movement. In virtue of their relative frequency in different sectors of striatum, as well as the suggestion that they may participate in earlier stages of motor planning (*e.g.*, initiation), these units appear good candidates for striosomal neurons *in the putamen.* Kimura (1984, 1986) has also studied behaviorally contingent neuronal responses in monkey putamen, ones with activation properties similar to those studied by Rolls et al. (1983) in the caudate nucleus. He has noted that the response contingencies of the putamen and the caudate nucleus units are similar, but that their resting discharge properties differ markedly- those in the putamen are tonically active, while those studied by Rolls in the caudate nucleus are not (Kimura, 1986). This kind of difference between spontaneous discharge, but not activation contingencies, is precisely what one would expect if comparing tissue with similar input, but of different type- such as dorsal striosomes and ventral matrix.

[17]Although their recordings in the putamen were principally lateral to those in the caudate nucleus, it seem likely that putamen and caudate nucleus in the monkey are somewhat ordered by the dorsal fill-ventral avoid constraint given (1) that most dorsal fill-ventral avoid transitions in cat in fact run dorsomedial to ventrolateral; (2) the temporalization of monkey striatum; and (3) our observation of corticostriatal input from 'area 6' that fills some striosomes in the sensory motor-recipient caudate nucleus and avoids them more centrally (see Fig. 6-9).

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References

Aggleton, J.P. (1985) A description of intra-amygdaloid connections in old world monkeys. *Exp. Brain Res.* **57,** 390-399.

Aggleton, J.P. and Mishkin, M. (1983) Memory impairments following restricted medial thalamic lesions in monkeys. *Exp. Brain Res.* **52,** 199-209.

Aggleton, J.P. and Passingham, R.E. (1981) Syndrome produced by lesions of the amygdala in monkeys (*Macaca mulatta*). *J. Comp. Physiol. Psychol.* **95,** 961-977.

Agid, Y., Bonnet, A.-M., Signoret, J.-L. and Lhermitte, F. (1979) Clinical, pharmacological, and biochemical approach of 'onset- and end-of-dose' dyskinesias. In *Advances in Neurology Vol. 24 The Extrapyramidal System and its Disorders* (Edited by L.J. Poirier, T.L. Sourkes and P.J. Bedard) pp. 401-410. Raven Press, New York.

Alexander, G.E. (1987) Selective neuronal discharge in monkey putamen reflects intended direction of planned limb movements. *Exp. Brain Res.* **67,** 623-634.

Alexander, G.E., DeLong, M.R. and Strick, P.L. (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. In *Annual Review of Neuroscience Vol. 9* (Edited by W.M. Cowan, E.M. Shooter, C.F. Stevens and R.F. Thompson) pp. 357-381. Annual Reviews, Palo Alto, CA.

Altman, J. and Bayer, S.A. (1979) Development of the diencephalon in the rat. IV. Quantitative study of the time of origin of neurons and the internuclear chronological gradients in the thalamus. *J. Comp. Neurol.* **188,** 455-472.

Altman, J. and Bayer, S.A. (1979) Development of the diencephalon in the rat. VI. Re-evaluation of the embryonic development of the thalamus on the basis of thymidine-radiographic datings. *J. Comp. Neurol.* **188,** 501-524.

Amaral, D.G. (1986) Amygdalohippocampal and amygdalocortical projections in the primate brain. In *Excitatory Amino Acids and Epilepsy,* (Edited by R. Schwarcz and Yehezdel-Ari) pp. 3-17. Plenum Press, New York.

Amaral, D.G. and Price, J.L. (1984) Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). *J. Comp. Neurol.* **230,** 465-496.

Amaral, D.G., Insausti, R. and Cowan, W.M. (1983) Evidence for a direct projection from the superior temporal gyrus to the entorhinal cortex in the monkey. *Brain Res.* **275,** 263-277.

Anderson, M.E. and DeVito, J.L. (1982) Sources of information converging with basal ganglia or cerebellar input to the thalamus. *Neursci. Abstr.* **8,** 170.

Angevine, J.B. (1970) Time of neuron origin in the diencephalon of the mouse. An autoradiographic study. *J. Comp. Neurol.* **139,** 129-188.

Angevine, J.B., and McConnell, J.A. (1974) Time of origin of striatal neurons in the mouse: an autoradiographic study. *Anat. Rec.* **178,** 300.

Ariens Kappers, C.U., Huber, G.C. and Crosby, E.C. (1960) *The Comparative Anatomy of the Nervous System of Vertebrates, Including Man.* Hafner, New York.

Avendano, C., Rausell, E. and Reinoso-Suarez, F. (1985) Thalamic projections to areas 5a and 5b of the parietal cortex in the cat: a retrograde horseradish peroxidase study. *J. Neurosci.* **5,** 1446-1470.

Azmitia, E.C. and Segal, M. (1978) An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. *J. Comp. Neurol.* **179,** 641-668.

Babb, R.S., Waters, R.S. and Asanuma, H. (1984) Corticocortical connections to the motor cortex from the posterior parietal lobe (areas 5a,5b,7) in the cat demonstrated by the retrograde axonal transport of horseradish peroxidase. *Exp. Brain Res.* **54,** 476-484.

Barbas, H. (1986) Pattern in the laminar origin of corticocortical connections. *J. Comp. Neurol.* **252,** 415-422.

Bard, P. and Mountcastle, V. (1948) Some forebrain mechanisms involved in expression of rage with special reference to suppression of angry behavior. In *Research Publications for Nervous and Mental Disease Vol. 27 The Frontal Lobes* (Edited by J.F. Fulton, C.D. Aring and S.B. Wortis) pp. 362-404. Williams and Wilkins, Baltimore.

Basbaum, A.I., Clanton, C.H. and Fields, H.L. (1976) Ascending projections of nucleus gigantocellularis and nucleus raphe magnus in the cat. An autoradiographic study. *Anat. Rec.* **184,** 354.

Basbaum, A.I., Clanton, C.H. and Fields, H.L. (1978) Three bulbospinal pathways from the rostral medulla of the cat: An autoradiographic study of pain modulating systems. *J. Comp. Neurol.* **178,** 209-224.

Battig, K., Rosvold, H.E. and Mishkin, M. (1960) Comparison of the effects of frontal and caudate lesions on delayed response and delayed alternation in monkeys. *J. Comp. Physiol. Psychol.* **53,** 400-404.

Beckstead, R.M. (1976) Convergent thalamic and mesencephalic projections to the anterior medial cortex in the rat. *J. Comp. Neurol.* **166,** 403-416.

Beckstead, R.M. (1984a) The thalamostriatal projection in the cat. *J. Comp. Neurol.* **223,** 313-346.

Beckstead, R.M. (1984b) A projection to the striatum from the medial subdivision of the posterior group of the thalamus in the cat. *Brain Res.* **300,** 351-356.

Beckstead, R.M., Domesick, V.B. and Nauta, W.J.H. (1979) Efferent connections of the substantia nigra and ventral tegmental area in the rat. *Brain Res.* **175,** 191-217.

Benedek, G., Jang, E.K. and Hicks, T.P. (1986) Physiological properties of visually responsive neurones in the insular cortex of the cat. *Neurosci. Lett.* **64,** 269-274.

Berman, N. (1977) Connections of the pretectum in the cat. *J. Comp. Neurol.* **174,** 227-254.

Berman, A. L. and Jones, E.G. (1982) *The Thalamus and Basal Telencephalon of the Cat. A Cytoarchitectonic Atlas with Stereotaxic Coordinates.* Univ. of Wisconsin Press, Madison.

Berrevoets, C.E. and Kuypers, H.G.J.M. (1975) Pericruciate cortical neurons projecting to brain stem reticular formation, dorsal column nuclei and spinal cord in the cat. *Neurosci. Lett.* **1,** 257-262.

Berson, D.M. (1980) *Extrageniculate and extrastriate affiliates of the geniculocortical pathway in the cat.* Doctoral dissertation, Mass. Inst. Tech., Cambridge, MA.

Besson, M.-J., Graybiel, A.M. and Nastuk, M. (1988) [^{3}H]-SCH23390 binding to D1 dopamine receptors in the basal ganglia of the cat and primate: delineation of striosomal compartments and pallidal and nigral subdivisions. *Neuroscience* (in the press).

Biedenbach, M.A. and DeVito, J.L. (1980) Origin of the pyramidal tract determined with horseradish peroxidase. *Brain Res.* **193,** 1-17.

Bleier, R. (1961) *The Hypothalamus of the Cat. A Cytoarchitectonic Atlas in the Horsley-Clarke Co-ordinate System.* Johhs Hopkins Press, Baltimore, MD.

Bobillier, P., Petitjean, F., Salvert, D., Ligier, M. and Sequin, S. (1975) Differential projections of the nucleus raphe dorsalis and nucleus raphe centralis as revealed by autoradiography. *Brain Res.* **85,** 205-210.

Bolam, J.P., Izzo, P.N. and Graybiel, A.M. (1987) Cellular substrate of the histochemically-defined striosome/matrix system of the caudate nucleus: a combined Golgi and immunocytochemical study in cat and ferret. *Neuroscience* (in the press).

Bonin, G.v. (1950) *Essay on the Cerebral Cortex.* Charles C. Thomas, Springfield, IL.

Bowman, E. and Olson, C.R. (1986) Visual and auditory association areas of cat posterior ectosylvian gyrus. *Neurosci. Abstr.* **12,** 1365.

Brooks, B.A., Fuchs, A.F. and Finocchoi, D. (1986) Saccadic eye movement deficits in the MPTP monkey model of Parkinson's disease. *Brain Res.* **383,** 402-407.

Brown, R.G. and Marsden, C.D. (1986) Visuospatial function in Parkinson's disease. *Brain* **109,** 987-1002.

Bucy, P.C. and Buchanan, D.N. (1932) Athetosis. *Brain* **55,** 479-492.

Burke, D., Knowles, L., Andrews, C. and Ashby, P. (1972) Spasticity, decerebrate rigidity and the clasp-knife phenomenon: an experimental study in the cat. *Brain* **95,** 31-48.

Burton, H. and Earls, F. (1969) Cortical representation of the ipsilateral chorda tympani nerve in the cat. *Brain Res.* **16,** 520-523.

Burton, H. and Kopf, E.M. (1984) Connections between the thalamus and the somatosensory areas of the anterior ectosylvian gyrus in the cat. *J. Comp. Neurol.* **224,** 173-205.

Burton, H. and Kopf, E.M. (1984) Ipsilateral cortical connections from the second and fourth somatic sensory areas in the cat. *J. Comp. Neurol.* **225,** 527-553.

Carlsen, J., Zaborszky, L. and Heimer, L. (1985) Cholinergic projections from the basal forebrain to the basolateral amygdaloid complex: a combined retrograde fluorescent and immunohistochemical study. *J. Comp. Neurol.* **234,** 155-167.

Carman, J.B., Cowan, W.M. and Powell, T.P.S. (1963) The organisation of the cortico-striate connexions in the rabbit. *Brain* **86,** 525-562.

Carman, J.B., Cowan, W.M., Powell, T.P.S. and Webster, K.E. (1965) A bilateral cortico-striate projection. *J. Neurol. Neurosurg. Psychiat.* **28,** 71-77.

Carpenter, M.B. (1961) Brain stem and infratentorial neuraxis in experimental dyskinesia. *Arch. Neurol.* **5,** 504-524.

Carpenter, M.B. and Brittin, G.M. (1958) Subthalamic hyperkinesia in rhesus monkey. Effect of secondary lesions in red nucleus and brachium conjunctivum. *J. Neurophysiol.* **21,** 400-413.

Carpenter, M.B., Whittier, J.R. and Mettler, F.A. (1950) Analysis of choreoid hyperkinesia in the rhesus monkey. Surgical and pharmacological analysis of hyperkinesia resulting from lesions in the subthalamic nucleus of Luys. *J. Comp. Neurol.* **92,** 293-331.

Carpenter, M.B., Correll, J.W. and Hinman, A. (1960) Spinal tracts mediating subthalamic hyperkinesia. Physiological effects of partial selective cordotomies upon dyskinesias in the rhesus monkey. *J. Neurophysiol.* **23,** 288-304.

Carpenter, M.B., Nakano, K. and Kim, R. (1976) Nigrothalamic projections in the monkey demonstrated by autoradiographic technics. *J. Comp. Neurol.* **165,** 401-416.

Castiglioni, A.J., Gallaway, M.C. and Coulter, J.D. (1978) Spinal projections from the midbrain in monkey. *J. Comp. Neurol.* **178,** 329-346.

Catsman-Berrevoets, C.E. and Kuypers, H.G.J.M. (1976) Cells of origin of cortical projections to dorsal column nuclei, spinal cord and bulbar medial reticular formation in the rhesus monkey. *Neurosci. Lett.* **3,** 245-252.

Cavada, C. and Reinoso-Suarez, F. (1985) Topographical organization of the cortical afferent connections of the prefrontal cortex in the cat. *J. Comp. Neurol.* **242,** 293-324.

Chase, T.N., Wexler, N.S. and Barbeau, A. (Editors) (1979) *Advances in Neurology.* Vol. 23 *Huntington's Disease.* Raven Press, New York.

Cheramy, A., Leviel, V., Daudet, F., Guibert, B., Chesselet, M.F. and Glowinski, J. (1981) Involvement of the thalamus in the reciprocal regulation of the two nigrostriatal dopaminergic pathways. *Neuroscience* **6,** 2657-2668.

Cheramy, A., Chesselet, M.F., Romo, R., Leviel, V. and Glowinski, J. (1983) Effects of unilateral electrical stimulation of various thalamic nuclei on the release of dopamine fron dendrites and nerve terminals of neurons of the two nigrostriatal dopaminergic pathways. *Neuroscience* **8,** 767-780.

Chesselet, M.F. and Graybiel, A.M. (1986) Striatal neurons expressing somatostatin-like immunoreactivity: evidence for a peptidergic interneuronal system in the cat. *Neuroscience* **17,** 547-571.

Chi, C.G. (1970) An experimental silver study of the ascending projections of the central gray substance and adjacent tegmentum in the rat with observations in the cat. *J. Comp. Neurol.* **139,** 259-272.

Christie, M.J., Summers, R.J., Stephenson, J.A., Cook, C.J. and Bear, P.M. (1987) Excitatory amino acid projections to the nucleus accumbens septi in the rat: a retrograde transport study utilizing D[^{3}H]aspartate and [^{3}GABA. *Neuroscience* **22,** 425-439.

Chronister, R.B. and DeFrance, J.F. (Editors) (1981) *The Neurobiology of the Nucleus Accumbens.* Haer Institute, Brunswick, Maine.

Chronwall, B.M., DiMaggio, D.A., Massari, V.J., Pickel, V.M., Ruggiero, D.A. and O'Donohue, T.L. (1985) The anatomy of neuropeptide-Y-containing neurons in rat brain. *Neuroscience* **15,** 1159-1181.

Conrad, L.C.A. and Pfaff, D.W. (1976a) Efferents from medial basal forebrain and hypothalamus in the rat. I. An autoradiographic study of the medial preoptic area. *J. Comp. Neurol.* **169,** 185-220.

Conrad, L.C.A. and Pfaff, D.W. (1976b) Efferents from medial basal forebrain and hypothalamus in the rat. II. An autoradiographic study of the anterior hypothalamus. *J. Comp. Neurol.* **169,** 221-262.

Corin, M.S., Elizan, T.S. and Bender, M.B. (1972) Oculomotor function in patients with Parkinson's disease. *J. Neurol. Sci.* **15,** 251-265.

Cornwall, J., Griffiths, A.C. and Phillipson, O.T. (1985) Inputs to paraventricular nucleus of the thalamus in the rat. *Neurosci. Lett. Suppl.* **22,** S74.

Cowan, W.M. and Powell, T.P.S. (1955) The projection of the midline and intralaminar nuclei of the thalamus of the rabbit. *J. Neurol. Neurosurg. Psychiat.* **18,** 266-279.

Cowan, W.M. and Powell, T.P.S. (1966) Strio-pallidal projection in the monkey. *J. Neurol. Neurosurg. Psychiat.* **29,** 426-439.

Cowan, W.M., Gottlieb, D.E., Hendrickson, A.E., Price, J.L. and Woolsey, T.A. (1972) The autoradiographic demostration of axonal connections in the central nervous system. *Brain Res.* **37,** 21-51.

Craig, A.D. and Burton, H. (1985) The distribution and topographical organization in the thalamus of anterogradely-transported horseradish peroxidase after spinal injections in cat and raccoon. *Exp. Brain Res.* **58,** 227-254.

Crosby, E.C., Humphrey, T. and Lauer, E. (1962) *Correlative Anatomy of the Nervous System.* Macmillan, New York.

Crosby, E.C., DeJonge, B.R. and Schneider, R.C. (1967) Evidence for some of the trends in the phylogenetic development of the vertebrate telencephalon. In *Evolution of the Forebrain. Phylogenesis and Ontogenesis of the Forebrain*, (Edited by R. Hassler and H. Stephan) pp. 117-135. Plenum Press, New York.

Crutcher, M.D. and DeLong, M.R. (1984) Single cell studies of the primate putamen. I. Functional organization. *Exp. Brain Res.* **53,** 233-243.

Dahlstrom, A. and Fuxe, K. (1964) Evidence for the existence of monoamine containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. *Acta Physiol. Scand.* **62 [Suppl. 232],** 1-55.

de Olmos, J. and Heimer, L. (1977) Mapping of collateral projections with the HRP-method. *Neurosci. Lett.* **6,** 107-114.

de Olmos, J. and Ingram, W.R. (1972) The projection field of the stria terminalis in the rat brain. An experimental study. *J. Comp. Neurol.* **146,** 303-334.

DeJong, J.D. and Melvill Jones, G. (1971) Akinesia, hypokinesia and bradykinesia in the oculomotor system of patients with Parkinson's disease. *Exp. Neurol.* **32,** 58-68.

DeLong, M.R. (1971) Activity of pallidal neurons during movement. *J. Neurophysiol.* **34,** 414-427.

DeLong, M.R., Georgopoulos, A.P. and Crutcher, M.D. (1983) Cortico-basal ganglia relations and coding of motor performance. *Neurosci. Lett. Suppl.* **7,** 30-40.

DeLong, M.R., Crutcher, M.D. and Georgopoulos, A.P. (1985) Primate globus pallidus and subthalamic nucleus: functional organization. *J. Neurophysiol.* **53,** 530-543.

Denny-Brown, D. (1962) *The Basal Ganglia and Their Relation to Disorders of Movement.* Oxford Univ. Press, London.

Denny-Brown, D. and Yanagisawa, N. (1976) The role of the basal ganglia in the initiation of movement. In *Res. Publ. Assoc. Res. Nerv. Ment. Dis. Vol. 55 The Basal Ganglia* (Edited by M.D. Yahr) pp. 115-149. Raven Press, New York.

DeVito, J.L. and Smith (1964) Subcortical projections of the prefrontal lobe of the monkey. *J. Comp. Neurol.* **123,** 413-424.

Diamond, I.T. (1983) Parallel pathways in the auditory, visual and somatic systems. In *Somatosensory Integration in the Thalamus. A Re-evaluation Based on the New Methodological Approaches*, (Edited by G. Macchi, A. Rustioni, and R. Spreafico) pp. 251-272. Elsevier, Amsterdam.

DiFiglia, M. and Graveland, G.A. (1983) Neuronal organization in the monkey neostriatum: a quantitative light microscopic study using semi-thick serial sections. *Neurosci. Abstr.* **9,** 659.

Divac, I., Rosvold, H.E. and Szwarcbart, M.K. (1967) Behavioural effects of selective abaltion of the caudate nucleus. *J. Comp. Physiol. Psychol.* **63,** 184-190.

Donoghue, J.P. and Herkenham, M. (1986) Neostriatal projections from individual cortical fields conform to histochemically distinct striatal compartments in the rat. *Brain Res.* **365,** 397-403.

Droogleever-Fortuyn, J. and Stephans, R. (1951) On the anatomical relations of the intralaminar and midline cells of the thalamus. *Electroenceph. Clin. Neurophysiol.* **3,** 393-400.

Dubner, R. and Brown, F.J. (1968) Response of cells to restricted visual stimuli in an association area of cat cerebral cortex. *Exp. Neurol.* **20,** 70-86.

Early, T.S., Reiman, E.M., Raichle, M.E. and Spitznagel, E.L. (1987) Left globus pallidus abnormality in never-medicatd patients with schizophrenia. *Proc. Natl. Acad. Sci.* **84,** 561-563.

Edwards, S.B. and de Olmos, J.S. (1976) Autoradiographic studies of the projections of the midbrain reticular formation: ascending projections of nucleus cuneiformis. *J. Comp. Neurol.* **165,** 417-432.

Edwards, S.B. and Hendrickson, A. (1981) The autoradiographic tracing of axonal connections in the central nervous system. In *Neuroanatomical Tract-tracing Methods*, (Edited by L. Heimer and M.J. RoBards) pp. 171-206. Plenum Press, New York.

Emson, P.C., Paxinos, G., Le Gal La Salle, G., Ben-Ari, Y. and Silver, A. (1979) Choline acetyltransferase and acetylcholinesterase containing projections from the basal forebrain to the amygdaloid complex of the rat. *Brain Res.* **165,** 271-282.

Engberg, I., Lundberg, A. and Ryall, R.W. (1968) Reticulospinal inhibition of transmission in reflex pathways. *J. Physiol.* **194,** 201-223.

Evarts, E.V., Teravainen, H. and Calne, D.B. (1981) Reaction time in Parkinson's disease. *Brain* **104,** 167-186.

Fallon, J.H., Koziell, D.A. and Moore, R.Y. (1978) Catecholamine innervation of the basal forebrain. II. Amygdala, suprarhinal cortex and entorhinal cortex. *J. Comp. Neurol.* **180,** 509-532.

Fass, B., Talbot, K. and Butcher, L.L. (1984) Evidence that efferents from the basolateral amygdala innervate the dorsolateral neostriatum in rats. *Neurosci. Lett.* **44,** 71-75.

Faull, R.L.M. and Villiger, J.W. (1986) Heterogeneous distribution of benzodiazepine receptors in the human striatum: a quantitative autoradiographic study comparing the pattern of receptor labelling with the distribution of acetylcholinesterase staining. *Brain Res.* **381,** 153-158.

Fentress, J.C., Stanfield, B.B. and Cowan, W.M. (1981) Observations on the development of the striatum in mice and rats. *Anat. Embryol.* **163,** 275-298.

Fernandez, V. and Hermes, B. (1973) Autoradiographic study of the development of the medial thalamic nuclei in the rabbit. *Brain Behav. Evol.* **7,** 453-465.

Ferrante, R.J. and Kowall, N.W. (1987) Tyrosine hydroxylase-like immunoreactivity is distributed in the matrix compartment of normal human and Huntington's disease striatum. *Brain Res.* **416,** 141-146.

Fox, C.A. (1940) Certain basal telencephalic centers in the cat. *J. Comp. Neurol.* **72,** 1-62.

Fox, C.A. (1943) The stria terminalis, longitudinal association bundle and precommissural fornix in the cat. *J. Comp. Neurol.* **79,** 277-295.

Fuller, T.A., Russchen, F.T. and Price, J.L. (1987) Sources of presumptive glutamergic/aspartergic afferents to the rat ventral striatopallidal region. *J. Comp. Neurol.* **258,** 317-338.

Fuxe, K. (1965) Evidence for the existence of monoamine containing neurons in the central nervous system. IV. Distribution of monoamine nerve terminals in the central nervous system. *Acta Physiol. Scand.* **64,** 39-85.

Gaffan, D. (1974) Recognition impaired and association intact in the memory of monkeys after transection of the fornix. *J. Comp. Physiol. Psychol.* **86,** 1100-1109.

Garcia-Rill, E. (1986) The basal ganglia and the locomotor regions. *Brain Res. Rev.* **11,** 47-63.

Garcia-Rill, E., Nieto, A., Adinolfi, A., Hull, C.D. and Buchwald, N.A. (1979) Projections to the neostriatum from cat precruciate cortex. Anatomy and physiology. *Brain Res.* **170,** 393-407.

Garraghty, P.E., Pons, T.P., Huerta, M.F. and Kaas, J.H. (1987) Somatotopic organization of the third somatosensory area (SIII) in cats. *Somatosens. Res.* **4,** 333-357.

Geneser-Jensen, F.A. and Blackstad, J.W. (1971) Distribution of acetylcholinesterase in the hippocampal region of the guinea pig. I. Entorhinal area, para subiculum and presubiculum. *Z. Zellforsch. Mikrosk. Anat.* **114,** 460-481.

Gerfen, C.R. (1984) The neostriatal mosaic: relationships among striatal input, output and peptidergic systems. *Nature* **311,** 461-464.

Gerfen, C.R. (1985) The neostriatal mosaic. I. Compartmental organization of projections from the striatum to the substantia nigra in the rat. *J. Comp. Neurol.* **236,** 454-476.

Gerfen, C.R., O'Leary, D.D.M. and Cowan, W.M. (1982) A note on the transneuronal transport of wheat germ agglutinin-conjugated horseradish peroxidase in the avian and rodent visual systems. *Exp. Brain Res.* **48,** 443-448.

Gerfen, C.R., Baimbridge, K.G. and Miller, J.J. (1985) The neostriatal mosaic: Compartmental distribution of calcium-binding protein and parvalbumin in the basal ganglia of the rat and monkey. *Proc. Natl. Acad. Sci. U.S.A.* **82,** 8780-8784.

Gerfen, C.R., Herkenham, M. and Thibault, J. (1987) The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *J. Neurosci.* **7,** 3915-3934.

Glees, P. (1944) The anatomical basis of cortico-striate connexions. *J. Anat.* **78,** 47-51.

Goedert, M., Mantyh, P.W., Hunt, S.P. and Emson, P.C. (1983) Mosaic distribution of neurotensin-like immunoreactivity in the cat striatum. *Brain Res.* **274,** 176-179.

Goedert, M., Mantyh, P.W., Hunt, S.P. and Emson, P.C. (1984) Inverse relationship between neurotensin receptors and neurotensin-like immunoreactivity in cat striatum . *Nature* **307,** 543-546.

Goldman, P.S. and Nauta, W.J.H. (1977) An intricately patterned prefronto-caudate projection in the rhesus monkey. *J. Comp. Neurol.* **171,** 369-386.

Goldman-Rakic, P.S. (1982) Cytoarchitectonic heterogeneity of the primate neostriatum: subdivision into island and matrix cellular compartments. *J. Comp. Neurol.* **205,** 398-413.

Graham, J. (1977) An autoradiographic study of the efferent connections of the superior colliculus in the cat. *J. Comp. Neurol.* **173,** 629-654.

Graham, J., Lin, C.-S. and Kaas, J.H. (1979) Subcortical projections of six visual cortical areas in the owl monkey, *Aotus trivirgatus. J. Comp. Neurol.* **187,** 557-580.

Graybiel, A.M. (1972a) Some ascending connections of the pulvinar and nucleus lateralis posterior of the thalamus in the cat. *Brain Res.* **44,** 99-125.

Graybiel, A.M. (1972b)Some fiber pathways related to the posterior thalamic region in the cat. *Brain Behav. Evol.* **6,** 363-393.

Graybiel, A.M. (1973) The thalamo-cortical projection of the so-called posterior nuclear group: a study with anterograde degeneration methods in the cat. *Brain Res.* **49,** 229-244.

Graybiel, A.M. (1975) Wallerian degeneration and anterograde tracer methods. In *The Use of Axonal Transport for Studies of Neuronal Connectivity,* (Edited by Cowan, W.M. and Cuenod, M.) pp. 174-216. Elsevier, Amsterdam.

Graybiel, A.M. (1977a) Organization of oculomotor pathways in the cat and rhesus monkey. In *Control of Gaze by Brain Stem Neurons,* (Edited by Baker, R. and Berthoz, A.) pp. 79-88. Elsevier, Amsterdam.

Graybiel, A.M. (1977b) Direct and indirect preoculomotor pathways of the brainstem: an autoradiographic study of the pontine reticular formation in the cat. *J. Comp. Neurol.* **175,** 37-78.

Graybiel, A.M. (1978) Organization of the nigrotectal connection: an experimental tracer study in the cat. *Brain Res.* **153,** 339-348.

Graybiel, A.M. (1984) Correspondence between the dopamine islands and striosomes of the mammalian striatum. *Neuroscience* **13,** 1157-1187.

Graybiel, A.M. and Berson, D.M. (1980) Histochemical identification and afferent connections of subdivisions in the lateralis posterior-pulvinar complex in the cat. *Neuroscience* **5,** 1175-1238.

Graybiel, A.M. and Chesselet, M.-F. (1984) Compartmental distribution of striatal cell bodies expressing [Met]enkephalin-like immunoreactivity. *Proc. Natl. Acad. Sci.* **81,** 7980-7984.

Graybiel, A.M. and Hickey, T.L. (1982) Chemospecificity of ontogenic units in the striatum: demonstration by combining [3H]thymidine neuronography and histochemical staining. *Proc. Natl. Acad. Sci. U.S.A.* **79,** 198-202.

Graybiel, A.M. and Ragsdale, C.W.(1978a) Striosomal organization of the caudate nucleus: I. Acetylcholinesterase histochemistry of the striatum in the cat, rhesus monkey and human being. *Neurosci. Abstr.* **4,** 44.

Graybiel, A.M. and Ragsdale, C.W.(1978b) Histochemically distinct compartments in the striatum of the human, monkey and cat demonstrated by acetylcholinesterase staining. *Proc. Natl. Acad. Sci.* **75,** 5723-5726.

Graybiel, A.M. and Ragsdale, C.W. (1979) Fiber connections of the basal ganglia. In *Progress in Brain Research Vol. 51 Development and Chemical Specificity of Neurons* (Edited by M. Cuenod, G.W. Kreutzberg and F.E. Bloom) pp. 239-283. Elsevier, Amsterdam.

Graybiel, A.M. and Ragsdale, C.W. (1983) Biochemical anatomy of the striatum. In *Chemical Neuroanatomy,* (Edited by P.C. Emson) pp. 427-504. Raven Press, New York.

Graybiel, A.M., Ragsdale, C.W. and Moon Edley, S. (1979) Compartments in the striatum of the cat observed by retrograde cell-labelling. *Exp. Brain Res.* **34,** 189-195.

Graybiel, A.M., Ragsdale, C.W., Yoneoka, E.S. and Elde, R.P. (1981) An immunohistochemical study of enkephalins and other neuropeptides in the striatum of the cat with evidence that the opiate peptides are arranged to form mosaic patterns in register with the striosomal compartments visible by acetylcholinesterase staining. *Neuroscience* **6,** 377-397.

Graybiel, A.M., Chesselet, M.-F., Wu, J.-Y., Eckenstein, F., and Joh, T.E. (1983) The relation of striosomes in the caudate nucleus of the cat to the organization of early-developing dopaminergic fibers, GAD-positive neuropil, and CAT-positive neurons. *Neurosci. Abstr.* **9,** 14.

Graybiel, A.M., Baughman, R.W. and Eckenstein, F. (1986) Cholinergic neuropil of the striatum observes striosomal boundaries. *Nature* **323,** 625-627.

Graybiel, A.M., Hirsch, E.C. and Agid, Y.A. (1987) Differences in tyrosine hydroxylase-like immunoreactivity characterize the mesostriatal innervation of striosomes and extrastriosomal matrix at maturity. *Proc. Natl. Acad. Sci.* **84,** 303-307.

Groenewegen, H.J. and Russchen, F.T. (1984) Organization of efferent projections of the nucleus accumbens to pallidal, hypothalamic, and mesencephalic structures: a tracing and immunohistochemical study in the cat. *J. Comp. Neurol.* **223,** 347-367.

Groenewegen, H.J., Room, P., Witter, M.P. and Lohman, A.H.M. (1980) Subcortical afferents of the nucleus accumbens septi in the cat, studied with retrograde axonal transport of horseradish peroxidase and bisbenzimid. *Neuroscience* **5,** 1903-1916.

Groenewegen, H.J., Room, P., Witter, M.P. and Lohman, A.H.M. (1982) Cortical afferents of the nucleus accumbens in the cat, studied with anterograde and retrograde transport techniques. *Neuroscience* **7,** 977-995.

Grove, E.A. (1987) *The neural associations of the substantia innominata in the rat.* Doctoral dissertation, Mass. Inst. Tech., Cambridge, MA.

Grove, E.A., and Ingham, C.A. (1986) Electron microscopic evidence of striatal input to intrapallidal neurons of cholinergic cell group Ch4 in the rat. *Neurosci. Abstr.* **12,** 1328.

Grove, E.A., Haber, S.N., Domesick, V.B. and Nauta, W.J.H. (1983) Differential projections from AChe-positive and AChe-negative ventral-pallidum cells in the rat. *Neurosci. Abstr.* **9,** 16.

Grove, E.A., Domesick, V.B. and Nauta, W.J.H. (1986) Light microscopic evidence of striatal input to intrapallidal neurons of cholinergic cell group Ch4 in the rat: a study employing the anterograde tracer *Phaseolus vulgaris* leucoagglutinin (PHA-L). *Brain Res.* **367,** 379-384.

Guitton, D. and Mandl, G. (1978a)Frontal 'oculomotor' area in alert cat. I. Eye movements and neck activity evoked by stimulation. *Brain Res.* **149,** 295-312.

Guitton, D. and Mandl, G. (1978b)Frontal 'oculomotor' area in alert cat. II. Unit discharges associated with eye movements and neck muscle activity. *Brain Res.* **149,** 313-327.

Guldin, W.O. and Markowitsch, H.J. (1984) Cortical and thalamic afferent connections of the insular and adjacent cortex of the cat. *J. Comp. Neurol.* **229,** 393-418.

Gurdjian, E.S. (1927) The diencephalon of the albino rat. Studies on the brain of the rat. No. 2. *J. Comp. Neurol.* **43,** 1-114.

Haber, S.N. and Nauta, W.J.H. (1983) Ramifications of the globus pallidus in the rat as indicated by patterns of immunohistochemistry. *Neuroscience* **9,** 245-260.

Haber, S.N., Groenewegen, H.J., Grove, E.A. and Nauta, W.J.H. (1985) Efferent connections of the ventral pallidum: evidence of a dual striato pallidofugal pathway. *J. Comp. Neurol.* **235,** 322-335.

Haberly, L.B. and Price, J.L. (1978) Association and commissural fiber systems of the olfactory cortex of the rat. I. Systems originating in the piriform cortex and adjacent areas. *J. Comp. Neurol.* **178,** 711-740.

Hall, E. (1972) The amygdala of the cat: a Golgi study. *Z. Zellforsch. Mikrosk. Anat.* **134,** 439-458.

Hardy, H., Heimer, L., Switzer, R. and Watkins, D. (1976) Simultaneous demonstration of horseradish peroxidase and acetylcholinesterase. *Neurosci. Lett.* **3,** 1-5.

Harik, S.I. and Morris, P.L. (1973) The effects of lesions in the head of the caudate nucleus on spontaneous and L-DOPA induced activity in the cat. *Brain Res.* **62,** 270-285.

Harrison, P.J., Hultborn, H., Jankowska, E., Katz, R., Storai, B. and Zytnicki, D. (1984) Labelling of interneurones by retrograde transsynaptic transport of horseradish peroxidase from motoneurones in rats and cats. *Neurosci. Lett.* **45,** 15-19.

Harting, J.K., Huerta, M.F., Frankfurter, A.J., Strominger, N.L. and Royce, G.J. (1980) Ascending pathways from the monkey superior colliculus: an autoradiographic analysis. *J. Comp. Neurol.* **192,** 853-882.

Hassler, R. and Muhs-Clement, K. (1964) Architektonischer Aufbau des sensomotorischen und parietalen Cortex der Katze. *J. Hirnforsch.* **6,** 377-420.

Hassler, R., Mundinger, F. and Riechert, T. (1979) *Stereotaxis in Parkinson Syndrome.* Springer, Berlin.

Heath, C.J. (1970) Distribution of axonal degeneration following lesion of the posterior group of thalamic nuclei in the cat. *Brain Res.* **21,** 435-438.

Heath, C.J. and Jones, E.G. (1971) An experimental study of ascending connections from the posterior group of thalamic nuclei in the cat . *J. Comp. Neurol.* **141,** 397-426.

Heath, C.J. and Jones, E.G. (1971) The anatomical organization of the suprasylvian gyrus of the cat. *Ergebn. Anat. Entwicklungsgesch.* **45,** 1-64.

Heimer, L. and Wilson, R.D. (1975) The subcortical projections of the allocortex: similarities in the neural associations of the hippocampus, the piriform cortex, and the neocortex. In *Golgi Centennial Symposium Proceedings,* (Edited by M. Santini) pp. 177-193. Raven Press, New York.

Hendry, S.H.C., Jones, E.G. and Graham, J. (1979) Thalamic relay nuclei for cerebellar and certain related fiber systems in the cat. *J. Comp. Neurol.* **185,** 679-714.

Herkenham, M.(1978a) Intralaminar and parafascicular efferents to the striatum and cortex in the rat: an autoradiographic study. *Anat. Rec.* **190,** 420.

Herkenham, M.(1978b) The connections of the nucleus reuniens thalami: evidence for a direct thalamo-hippocampal pathway in the rat. *J. Comp. Neurol.* **177,** 589-610.

Herkenham, M. (1979) The afferent and efferent connections of the ventromedial thalamic nucleus in the rat. *J. Comp. Neurol.* **183,** 487-518.

Herkenham, M. (1980) Laminar organization of thalamic projections to the rat neocortex. *Science* **207,** 532-535.

Herkenham, M. (1986) New perspectives on the organization and evolution of nonspecific thalamocortical projections. In *Cerebral Cortex Vol. 5* (Edited by E.G. Jones and A. Peters) pp. 403-445. Plenum Press, New York.

Herkenham, M. and Pert, C.B. (1981) Mosaic distribution of opiate receptors, parafascicular projections and acetylcholinesterase in rat striatum. *Nature* **291,** 415-418.

Herkenham, M., Moon Edley, S. and Stuart, J. (1984) Cell clusters in the nucleus accumbens of the rat, and the mosaic relationship of opiate receptors, acetylcholinesterase and subcortical afferent terminals. *Neuroscience* **11,** 561-593.

Hikosaka, O. and Sakamoto, M. (1986) Cell activity in monkey caudate nucleus preceding saccadic eye movements. *Exp. Brain Res.* **63,** 659-662.

Hikosaka, O. and Wurtz, R.H. (1983a)Visual and oculomotor functions of monkey substantia nigra pars reticulata. I. Relation of visual and auditory responses to saccades. *J. Neurophysiol.* **49,** 1230-1253.

Hikosaka, O. and Wurtz, R.H. (1983b) Visual and oculomotor functions of monkey substantia nigra pars reticulata. II. Visual responses to fixation of gaze. *J. Neurophysiol.* **49,** 1254-1267.

Hikosaka, O. and Wurtz, R.H. (1983c) Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. *J. Neurophysiol.* **49,** 1268-1284.

Hikosaka, O. and Wurtz, R.H. (1983d) Visual and oculomotor functions of monkey substantia nigra pars reticulata. IV. Relation of substantia nigra to superior colliculus. *J. Neurophysiol.* **49,** 1285-1301.

Hikosaka, O. and Wurtz, R.H. (1985a) Modification of saccadic eye movements by GABA-related substances. I. Effect of muscimol and bicuculline in monkey superior colliculus. *J. Neurophysiol.* **53,** 266-291.

Hikosaka, O. and Wurtz, R.H. (1985b) Modification of saccadic eye movements by GABA-related substances. II. Effects of muscimol in monkey substantia nigra pars reticulata. *J. Neurophysiol.* **53,** 292-308.

Holstege, G., Kuypers, H.G.J.M. and Dekker, J.J. (1977) The organization of the bulbar fibre connections to the trigeminal, facial, and hypoglossal motor nuclei. II. An autoradiographic study in cat. *Brain* **100,** 265-286.

Hopkins, D.A., McLean, J.H. and Takeuchi, Y. (1981) Amygdalotegmental projections: light and electron microscopic studies utilizing anterograde degeneration and the anterograde and retrograde transport of horseradish peroxidase. In *The Amygdaloid Complex*, (Edited by Y. Ben-Ari) pp. 133-150. Elsevier, Amsterdam.

Horel, J.A., Keating, E.G. and Misantone, L.J. (1975) Partial Kluver-Bucy syndrome produced by destroying temporal neocortex or amygdala. *Brain Res.* **94,** 347-359.

Hu, H. and Jayaraman, A. (1986) The projection pattern of the suprageniculate nucleus to the caudate nucleus in cats. *Brain Res.* **368,** 201-203.

Huerta, M.F. and Harting, J.K. (1982) Tectal control of spinal cord activity: neuroanatomical demonstration of pathways connecting the superior colliculus with the cervical spinal cord grey. In *Progress in Brain Research Vol. 57 Anatomy of Descending Pathways to the Spinal Cord* (Edited by H.G.J.M. Kuypers and G.F. Martin) pp. 293-328. Elsevier, Amsterdam.

Illing, R.B. and Graybiel, A.M. (1985) Convergence of afferents from frontal cortex and substantia nigra onto acetylcholinesterase-rich patches of the cat's superior colliculus. *Neuroscience* **14,** 455-482.

Illing, R.B. and Wassle, H. (1979) Visualization of the HRP reaction product using the polarization microscope. *Neurosci. Lett.* **13,** 7-11.

Ingram, W.R., Hannett, F.I. and Ranson, S.W. (1932) The topography of the nuclei of the diencephalon of the cat. *J. Comp. Neurol.* **55,** 333-394.

Itaya, S.K. and Van Hoesen, G.W. (1982) WGA-HRP as a transneuronal marker in the visual pathways of monkey and rat. *Brain Res.* **236,** 199-204.

Itaya, S.K., Van Hoesen, G.W. and Barnes, C.L. (1986) Anterograde transsynaptic transport of WGA-HRP in the limbic system of rat and monkey. *Brain Res.* **398,** 397-402.

Itoh, K., Yasui, Y., Takada, M., Mitani, A., Kaneko, T., Sugimoto, T. and Mizuno, N. (1984) An anterograde-retrograde transneuronal transport of conjugates of wheat germ agglutinin with horseradish peroxidase(WGA-HRP): labeling of neurons in the reticular nucleus of the thalamus with WGA-HRP injected into the posterior column nuclei in the cat. *Brain Res.* **323,** 185-187.

Jacobowitz, D.M. and Palkovits, M. (1974) Topographic atlas of catecholamine and acetylcholinesterase-containing neurons in the rat brain. I. Forebrain (telencephalon, diencephalon). *J. Comp. Neurol.* **157,** 13-28.

Jayaraman, A. (1985) Organization of thalamic projections in the nucleus accumbens and the caudate nucleus in cats and its relation with hippocampal and other subcortical afferents. *J. Comp. Neurol.* **231,** 396-420.

Jayaraman, A., Batton, R.R. and Carpenter, M.B. (1977) Nigrotectal projections in the monkey: an autoradiographic study. *Brain Res.* **135,** 147-152.

Jeffers, I.M. and Olson, C.R. (1985) Somatomotor, oculomotor and high-order pathways through basal ganglia of cat. *Neurosci. Abstr.* **11,** 200.

Jimenez-Castellanos, J. and Graybiel, A.M. (1985) The dopamine-containing innervation of striosomes: nigral subsystems and their striatal correspondents. *Neurosci. Abstr.* **11,** 1249.

Jimenez-Castellanos, J. and Graybiel, A.M. (1987) Subdivisions of the dopamine-containing A8-A9-A10 complex identified by their differential mesostriatal innervation of striosomes and extrastriosomal matrix. *Neuroscience* **23,** 223-242.

Johnson, T.N. and Rosvold, H.E. (1971) Topographic projections on the globus pallidus and the substantia nigra of selectively placed lesions in the precommissural caudate nucleus and putamen in the monkey. *Exp. Neurol.* **33,** 584-596.

Johnson, T.N., Rosvold, H.E. and Mishkin, M. (1968) Projections from behaviourally-defined sectors of the prefrontal cortex to the basal ganglia, septum and diencephalon of the monkey. *Exp. Neurol.* **21,** 20-34.

Jones, E.G. (1985) *The Thalamus.* Plenum Press, New York.

Jones, E.G. and Burton, H. (1976) A projection from the medial pulvinar to the amygdala in primates. *Brain Res.* **104,** 142-147.

Jones. E.G. and Leavitt, R.Y. (1974) Retrograde axonal transport and the demonstration of non-specific projections to the cerebral cortex and striatum from the thalamic intralaminar nuclei in the rat, cat and monkey. *J. Comp. Neurol.* **154,** 349-378.

Jones, B. and Mishkin, M. (1972) Limbic lesions and the problem of stimulus-reinforcement associations. *Exp. Neurol.* **36,** 362-377.

Jones, E.G. and Powell, T.P.S. (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain* **93,** 793-820.

Jones, B.E. and Yang, T.-Z. (1985) The efferent projections from the reticular formation and the locus coeruleus studied by anterograde and retrograde axonal transport in the rat. *J. Comp. Neurol.* **242,** 56-92.

Jones, E.G., Coulter, J.D., Burton, H. and Porter, R. (1977) Cells of origin and terminal distribution of corticostriatal fibers arising in the sensory-motor cortex of monkeys. *J. Comp. Neurol.* **173,** 53-80.

Joyce, J.N., Sapp, D.W. and Marshall, J.F. (1986) Human striatal dopamine receptors are organized in compartments. *Proc. Natl. Acad. Sci.* **83,** 8002-8006.

Jung, R. and Hassler, R. (1960) The extrapyramidal motor system. In *Handbook of Physiology. Section 1: Neurophysiology Vol. II* (Edited by H.W. Magoun) pp. 863-927. American Physiological Soc., Washington, D.C.

Kaada, B.R. (1972) Stimulation and regional ablation of the amygdaloid complex with reference to functional representations. In *The Neurobiology of the Amygdala,* (Edited by B.E. Eleftheriou) pp. 205-282. Plenum Press, New York.

Kaitz, S.S. and Robertson, R.T. (1981) Thalamic connections with limbic cortex. II. Corticothalamic projections. *J. Comp. Neurol.* **195,** 527-545.

Kalil, K. (1978) Patch-like termination of thalamic fibers in the putamen of the rhesus monkey: an autoradiographic study. *Brain Res.* **140,** 333-339.

Kanazawa, I., Tanaka, Y. and Cho, F. (1986) 'Choreic' movement induced by unilateral kainate lesion of the striatum and L-DOPA administration in monkey. *Neurosci. Lett.* **71,** 241-246.

Kelley, A.E. and Domesick, V.B. (1982) The distribution of the projection from the hippocampal formation to the nucleus accumbens in the rat: an anterograde- and retrograde-horseradish peroxidase study. *Neuroscience* **7,** 2321-2335.

Kelley, A.E. and Stinus, L. (1984) The distribution of the projection from the parataenial nucleus of the thalamus to the nucleus accumbens in the rat: an autoradiographic study. *Exp. Brain Res.* **54,** 499-512.

Kelley, A.E., Domesick, V.B. and Nauta, W.J.H. (1982) The amygdalostriatal projection in the rat- an anatomical study by anterograde and retrograde tracing methods. *Neuroscience* **7,** 615-630.

Kelly, P.H., Seviour, P.W. and Iversen, S.D. (1975) Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Res.* **94,** 507-522.

Kemp, J. A. and Powell, T.P.S. (1970) The cortico-striate projection in the monkey. *Brain* **93,** 525-546.

Kemp, J. A. and Powell, T.P.S. (1971a) The structure of the caudate nucleus of the cat: light and electron microscopy. *Phil. Trans. R. Soc. Lond. [Biol.]* **262,** 383-401.

Kemp, J. A. and Powell, T.P.S. (1971b) The site of termination of afferent fibres in the caudate nucleus. *Phil. Trans. R. Soc. Lond. [Biol.]* **262,** 413-427.

Kemp, J. A. and Powell, T.P.S. (1971c) The termination of fibres from the cerebral cortex and thalamus upon dendritic spines in the caudate nucleus: a study with the Golgi method. *Phil. Trans. R. Soc. Lond. [Biol.]* **262,** 429-439.

Kemp, J. A. and Powell, T.P.S. (1971d) The connections of the striatum and globus pallidus: synthesis and speculation. *Phil. Trans. R. Soc. Lond. [Biol.]* **262,** 441-457.

Kievit, J. and Kuypers, H.G.J.M. (1977) Organization of the thalamocortical connections to the frontal lobe in the rhesus monkey. *Exp. Brain Res.* **29,** 229-322.

Kimura, M. (1986) The role of primate putamen neurons in the association of sensory stimuli with movement. *Neurosci. Res.* **3,** 436-443.

Kimura, M., Raijkowski, J. and Evarts, E. (1984) Tonically discharging putamen neurons exhibit set dependecnt responses. *Proc. Natl. Acad. Sci.* **81,** 4998-5001.

Kitai, S.T., Kocsis, J.D., Preston, R.J. and Sugimori, M. (1976) Monosynaptic inputs to caudate neurons identified by intracellular injection of horseradish peroxidase. *Brain Res.* **109,** 601-606.

Kitai, S.T., Kocsis, J.D. and Wood, J. (1976) Origin and characteristics of the cortico-caudate afferents: an anatomical and electrophysiological study. *Brain Res.* **118,** 137-141.

Kluver, H. and Bucy, P.C. (1939) Preliminary analysis of functions of the temporal lobe in monkeys. *Arch. Neurol. Psychiat.* **42,** 979-1000.

Koelle, G.B. (1954) The histochemical localization of cholinesterases in the central nervous system of the rat. *J. Comp. Neurol.* **100,** 211-236.

Kowall, N.W., Ferrante, R.J., Beal, M.F., Sofroniew, M.V., Cuello, A.C. and Martin, J.B. (1987) Neuropeptide Y, somatostatin, and reduced nicotinamide adenine dinucleotide phosphate diaphorase in human striatum: a combined immunocytochemical and enzyme histochemical study. *Neuroscience* **20,** 817-828.

Krauthamer, G.M. (1979) Sensory functions of the neostriatum . In *The Neostriatum*, (Edited by I. Divac, R. Oberg and E. Guanila) pp. 263-289. Pergamon Press, New York.

Krettek, J.E. and Price, J.L.(1977a) Projections from the amygdaloid complex to the cerebral cortex and thalamus in the rat and cat. *J. Comp. Neurol.* **172,** 687-722.

Krettek, J.E. and Price, J.L. (1977b) Projections from the amygdaloid complex and adjacent olfactory structures to the entorhinal cortex and to the subiculum in the rat and cat. *J. Comp. Neurol.* **172,** 723-752.

Krettek, J.E. and Price, J.L. (1978a) Amygdaloid projections to subcortical structures within the basal forebrain and brainstem in the rat and cat. *J. Comp. Neurol.* **178,** 225-254.

Krettek, J.E. and Price, J.L.(1978b) A description of the amygdaloid complex in the rat and cat, with observations on intra-amygdaloid axonal connections. *J. Comp. Neurol.* **178,** 255-280.

Kubozono, T., Nakano, K., Tokushige, A., Hasegawa, Y. and Kohno, M. (1986) Topographical organization of the projections from the cerebral cortex to the head of the caudate nucleus. A horseradish peroxidase study in the cat. *Neuroscience* **19,** 113-123.

Kunzle, H. (1975) Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. *Brain Res.* **88,** 195-210.

Kunzle, H. (1977) Projections from the primary somatosensory cortex to basal ganglia and thalamus in the monkey. *Exp. Brain Res.* **30,** 481-492.

Kunzle, H. and Akert, K. (1977) Efferent connections of cortical area 8 (frontal eye field) in *Macaca fascicularis.* A reinvestigation using the autoradiographic method. *J. Comp. Neurol.* **173,** 147-164.

Kuypers, H.G.J.M. (1981) Anatomy of descending pathways. In *Handbook of Physiology. Section I: The Nervous System Vol. II Motor Control* (Edited by J.M. Brookhart, V.B. Mountcastle and V.B. Brooks) pp. 597-666. American Physiological Soc., Washington, D.C.

Kuypers, H.G.J.M. and Lawrence, D.G. (1967) Cortical projections to the red nucleus and the brain stem in the rhesus monkey. *Brain Res.* **4,** 151-188.

Kuypers, H.G.J.M. and Maisky, V.A. (1975) Retrograde axonal transport of horseradish peroxidase from spinal cord to brain stem cell groups in the cat. *Neurosci. Lett.* **1,** 9-14.

Lashley, K.S. (1941) Thalamo-cortical connections of the rat's brain. *J. Comp. Neurol.* **95,** 67-121.

Laursen, A.M. (1963) *Acta Physiol. Scand..* Vol. 59 *Corpus Striatum.* Copenhagen.

Lawrence, D.G. and Kuypers, H.G.J.M. (1968a) The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. *Brain* **91,** 1-14.

Lawrence, D.G. and Kuypers, H.G.J.M. (1968b) The functional organization of the motor system in the monkey. II. The effects of lesions of the descending brain-stem pathways. *Brain* **91,** 15-36.

Le Gros Clark, W.E. and Russell, W.R. (1939) Observations of the efferent connexions of the centre median nucleus. *J. Anat.* **73,** 255-262.

Leviel, V., Chesselet, M.F., Glowinski, J. and Cheramy, A. (1981) Involvement of the thalamus in the asymmetrical effects of unilateral sensory stimuli on the two nigrostriatal dopaminergic pathways in the cat. *Brain Res.* **223,** 257-272.

Liles, S.L. (1979) Topographic organization of neurons related to arm movement in the putamen. In *Advances in Neurology Vol. 23 Huntington's Disease* (Edited by Chase, T.N., Wexler, N.S. and Barbeau, A.) pp. 155-162. Raven Press, New York.

Liles, S.L. (1985) Activity of neurons in putamen during active and passive movements of wrist. *J. Neurophysiol.* **53,** 217-236.

Liles, S.L. and Davis, G.D. (1969) Athetoid and choreiform hyperkinesias produced by caudate lesions in the cat. *Science* **164,** 195-197.

Lin, C.-S., May, P.J. and Hall, W.C. (1984) Non-intralaminar thalamostriatal projections in the grey squirrel (*Sciurus carolinensis*) and tree shrew (*Tupaia glis*). *J. Comp. Neurol.* **230,** 33-46.

Lindvall, O., Bjorklund, A., Nobin, A. and Steveni, U. (1974) The adrenergic innervation of the rat thalamus as revealed by the glyoxylic acid fluorescence method. *J. Comp. Neurol.* **154,** 317-348.

Loopuijt, L.D., Sebens, J.B. and Korf, J. (1987) A mosaic-like distribution of dopamine receptors in rat neostriatum and its relationship to striosomes. *Brain Res.* **405,** 405-408.

Lowenstein, P.R., Slesinger, P.A., Singer, H.S., Walker, L.C., Casanove, M.F., Price, D.L. and Coyle, J.T. (1987) An autoradiographic study of the development of [^{3}H]hemicholinium-3 binding sites in human and baboon basal ganglia: a marker for the sodium-dependent high affinity choline uptake system. *Dev. Brain Res.* **34,** 291-297.

Luskin, M.B. and Price, J.L. (1983) The topographic organization of associational fibers of the olfactory system in the rat, including centrifugal fibers to the olfactory bulb. *J. Comp. Neurol.* **216,** 264-291.

Macchi, G. (1983) Old and new anatomo-functional criteria in the subdivision of the thalamic nuclei . In *Somatosensory Integration in the Thalamus. A Re-evaluation Based on the New Methodological Approaches,* (Edited by G. Macchi, A. Rustioni, and R. Spreafico) pp. 3-15. Elsevier, Amsterdam.

Macchi, G., Bentivoglio, M., Rossini, P. and Tempesta, E. (1978) The basolateral amygdaloid projections to the neocortex in the cat. *Neurosci. Lett.* **9,** 347-351.

Macchi, G., Bentivoglio, M., Molinari, M. and Minciacchi, D. (1984) The thalamocaudate versus thalamocortical projections as studied in the cat with fluorescent retrograde double labeling. *Exp. Brain Res.* **54,** 225-239.

MacDonnell, M.F. and Flynn, J.P. (1964) Attack elicited by stimulation of the thalamus of the cat. *Science* **144,** 1249-1250.

Malach, R. and Graybiel, A.M. (1986) Mosaic architecture of the somatic sensory-recipient sector of the cat's striatum. *J. Neurosci.* **6,** 3436-3458.

Mantyh, P.W. (1983a) The terminations of the spinothalamic tract in the cat. *Neurosci. Lett.* **38,** 119-124.

Mantyh, P.W. (1983b) Connections of midbrain periaqueductal gray in the monkey. I. Ascending efferent projections. *J. Neurophysiol.* **49,** 567-581.

Marsden, C.D. (1982) The mysterious function of the basal ganglia. The Robert Wartenberg Lecture. *Neurology* **32,** 514-539.

Martin, J.P. and McCaul, I.R. (1959) Acute hemiballismus treated by ventrolateral thalamolysis. *Brain* **82,** 104-108.

Martin, G.F., Laxson, L.C., Panneton, W.M. and Tschismadia, I. (1979) Spinal projections from the mesencephalic and pontine reticular formation in the North American opossum: a study using axonal transport techniques. *J. Comp. Neurol.* **187,** 373-400.

Matthysse, S. (1974) Schizophrenia: relationships to dopamine transmission, motor control, and feature extraction. In *The Neurosciences: Third Study Program,* (Edited by F.O. Schmitt and F.G. Worden) pp. 733-737. M.I.T. Press, Cambridge, MA.

Maunsell, J.H.R. and Van Essen, D.C. (1983) The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. *J. Neurosci.* **3,** 2563-2586.

May, P.J. and Hall, W.C. (1984) Relationships between the nigrotectal pathway and the cells of origin of the predorsal bundle. *J. Comp. Neurol.* **226,** 357-376.

McAllister, J.P. and Das, G.D. (1977) Neurogenesis in the epithalamus, dorsal thalamus and ventral thalamus of the rat: an autoradiographic and cytological study. *J. Comp. Neurol.* **172,** 647-686.

Mehler, W.R. (1966) Further notes on the centromedian nucleus of Luys. In *The Thalamus,* (Edited by D.P. Purpura and M.D. Yahr) pp. 109-127. Columbia University Press, New York.

Mehler, W.R. (1982) The basal ganglia- circa 1982. *Appl. Neurophysiol.* **44,** 261-290.

Mehler, W.R., Pretorius, J.K., Phelan, K.D. and Mantyh, P.W. (1981) Diencephalic afferent connections of the amygdala in the squirrel monkey with observations and comments on the cat and rat. In *The Amygdaloid Complex*, (Edited by Y. Ben-Ari) pp. 105-120. Elsevier, Amsterdam.

Meibach, R.C. and Katzman, R. (1981) Origin, course and termination of dopaminergic substantia nigra neurons projecting to the amygdaloid complex in the cat. *Neuroscience* **6,** 2159-2171.

Mesulam, M.-M. (1978) Tetramethyl benzidine for horseradish peroxidase neurohistochemistry: a non-carcinogenic blue reaction product with superior sensitivity for visualizing neural afferents and efferents. *J. Histochem. Cytochem.* **26,** 106-117.

Mesulam, M.-M. (Editor) (1982) *IBRO Handbook Series: Methods in the Neurosciences. Tracing Neural Connections with Horseradish Peroxidase.* J. Wiley, New York.

Meyer, G. and Wahle, P. (1986) The olfactory tubercle of the cat. I. Morphological components. *Exp. Brain Res.* **62,** 515-528.

Mink. J.W. and Thach, W.T. (1987) Preferential relation of pallidal neurons to ballistic movements. *Brain Res.* **417,** 393-398.

Mishkin, M. (1978) Memory in monkeys severely impaired by combined but not separate removal of amygdala and hippocampus. *Nature* **273,** 297-298.

Mishkin, M. and Delacour, J. (1975) An analysis of short-term visual memory in the monkey. *J. Exp. Psychol.* **1,** 326-334.

Mogenson, G.J. and Yim, C.Y. (1981) Electrophysiological and neuropharmacological-behavioral studies of the nucleus accumbens: implications for its role as a limbic-motor interface. In *The Neurobiology of the Nucleus Accumbens*, (Edited by R.B. Chronister and J.F. DeFrance) pp. 210-229. Haer Institute, Brunswick, Maine.

Moon Edley, S. and Graybiel, A.M. (1983) The afferent and efferent connections of the feline nucleus tegmenti pedunculopontinus, pars compacta. *J. Comp. Neurol.* **217,** 187-215.

Moon Edley, S. and Herkenham, M. (1984) Heterogeneous dopaminergic projections to the neostriatum of the rat: nuclei of origin dictate relationship to opiate receptor patches. *Anat. Rec.* **208,** 120A.

Murphy, M.R., MacLean, P.D. and Hamilton, S.C. (1981) Species-typical behavior of hamsters deprived from birth of the neocortex. *Science* **213,** 459-461.

Murray, M. (1966) Degeneration of some intralaminar thalamic nuclei after cortical removals in the cat. *J. Comp. Neurol.* **127,** 341-368.

Murray, E.A. and Mishkin, M. (1985) Amygdalectomy impairs crossmodal association in monkeys. *Science* **228,** 604-606.

Musil, S.Y. and Olson, C.R. (1986) Cortical areas in the medial frontal lobe of the cat. *Neurosci. Abstr.* **12,** 1440.

Nakano, K., Kohno, M., Hasegawa, Y. and Tokushige, A. (1985) Cortical and brain stem afferents to the ventral thalamic nuclei of the cat demonstrated by retrograde axonal transport of horseradish peroxidase. *J. Comp. Neurol.* **231,** 102-120.

Narabayashi, H. and Kubota, K. (1966) Reconsideration of ventrolateral thalamotomy for hyperkinesis. In *Progress in Brain Research Vol. 21B Correlative Neurosciences. Part B: Clinical Studies* (Edited by T. Tokizane and J.P. Schade) pp. 339-349. Elsevier, Amsterdam.

Narabayashi, H., Yokochi, F. and Nakajima, Y. (1984) Levodopa-induced dyskinesia and thalamotomy. *J. Neurol. Neurosurg. Psychiat.* **47,** 831-839.

Nastuk, M.A. and Graybiel, A.M. (1985) Patterns of muscarinic cholinergic binding in the striatum and their relation to dopamine islands and striosomes. *J. Comp. Neurol.* **237,** 176-194.

Nastuk, M.A. and Graybiel, A.M. (1988) Autoradiographic localization and biochemical characteristics of M1 and M2 muscarinic binding sites in the striatum of the cat, monkey and human. *J. Neurosci.* (in the press).

Nauta, W.J.H. (1953) Some projections of the medial wall of the hemisphere in the rat's brain (cortical areas 32 and 25, 24 and 29). *Anat. Rec.* **115,** 352.

Nauta, W.J.H. (1958) Hippocampal projections and related neural pathways to the mid-brain in the cat. *Brain* **81,** 319-340.

Nauta, W.J.H. (1962) Neural associations of the amygdaloid complex in the monkey. *Brain* **85,** 505-521.

Nauta, W.J.H. (1964) Some efferent connections of the prefrontal cortex in the monkey. In *The Frontal Granular Cortex and Behavior,* (Edited by J.M. Warren and K. Akert) pp. 397-409. McGraw-Hill, New York.

Nauta, H.J.W. (1979) Projections of the pallidal complex: an autoradiographic study in the cat. *Neuroscience* **4,** 1853-1873.

Nauta, W.J.H. and Domesick, V.B. (1978) Crossroads of limbic and striatal circuitry: hypothalamo-nigral connections. In *Limbic Mechanisms*, (Edited by K.E. Livingston and O. Hornykiewicz) pp. 75-93. Plenum Press, New York.

Nauta, W.J.H. and Kuypers, H.G.J.M. (1958) Some ascending pathways in the brain stem reticular formation. In *Reticular Formation of the Brain*, (Edited by H.H. Jasper et al.) pp. 3-30. Little, Brown, Boston.

Nauta, W.J.H. and Mehler, W.R. (1966) Projections of the lentiform nuclei in the monkey. *Brain Res.* **1,** 3-42.

Nauta, W.J.H. and Whitlock, D.G. (1954) An anatomical analysis of the non-specific thalamic projection system. In *Brain Mechanisms and Consciousness*, (Edited by E.D. Adrian, F. Bremer and H.H. Jasper) pp. 81-116. Blackwell Scientific Publications, Oxford.

Nauta, W.J.H., Smith, G.P., Faull, R.L.M. and Domesick, V.B. (1978) Efferent connections and nigral afferents of the nucleus accumbens septi in the rat. *Neuroscience* **3,** 385-401.

Newman, R. and Winans, S.S. (1980) An experimental study of the ventral striatum of the golden hamster. I. Neuronal connections of the nucleus accumbens. *J. Comp. Neurol.* **191,** 167-192.

Nieoullon, A. and Rispal-Padel, L. (1976) Somatotopic localization in cat motor cortex. *Brain Res.* **105,** 405-422.

Niimi, K. and Kuwahara, E. (1973) The dorsal thalamus of the cat and comparison with monkey and man. *J. Hirnforsch.* **14,** 303-326.

Niimi, K., Niimi, M. and Okada, Y. (1978) Thalamic afferents to the limbic cortex in the cat studied with the method of retrograde axonal transport of horseradish peroxidase. *Brain Res.* **145,** 225-238.

Niimi, K., Matsuoka, H., Aisaka, T. and Okada, Y. (1981) Thalamic afferents to the prefrontal cortex in the cat traced with horseradish peroxidase. *J. Hirnforsch.* **22,** 221-241.

Nyberg-Hansen, R. (1965) Sites and mode of termination of reticulospinal fibers in the cat. An experimental study with silver impregnation methods. *J. Comp. Neurol.* **124,** 71-100.

Oberg, R.G.E. and Divac, I. (1979) 'Cognitive' functions of the neostriatum . In *The Neostriatum*, (Edited by I. Divac, R. Oberg and E. Guanila) pp. 291-313. Pergamon Press, New York.

Oka, H. (1980) Organization of the cortico-caudate projections. A horseradish peroxidase study in the cat. *Exp. Brain Res.* **40,** 203-208.

Olson, C.R. and Graybiel, A.M. (1987) Ectosylvian visual area of the cat: location, retinotopic organization and connections. *J. Comp. Neurol.* **261,** 277-294.

Olson, C.R. and Jeffers, I.M. (1987) Organization of cortical and subcortical projections to area 6m of the cat. *J. Comp. Neurol.* **266,** 73-94.

Olson, C.R. and Lawler, K. (1987) Cortical and subcortical afferent connnections of a posterior division of feline area 7 (area 7p). *J. Comp. Neurol.* **259,** 13-30.

Olson, C.R., Krauzlis, R.J. and Lipkin, S.M. (1987) Areas 7 and 5 in cat: visual and somatosensory responses of single neurons and afferent sensory pathways. *Neurosci. Abstr.* **13,** 628.

Ottersen, O.P. and Ben-Ari, Y. (1979) Afferent connections to the amygdaloid complex of the rat and cat. I. Projections from the thalamus. *J. Comp. Neurol.* **187,** 401-424.

Pandya, D.N. and Seltzer, B. (1982) Intrinsic connections and architectonics of posterior parietal cortex in the rhesus monkey. *J. Comp. Neurol.* **204,** 196-210.

Papez, J.W. (1937) A proposed mechanism of emotion. *Arch. Neurol. Psychiat.* **38,** 725-744.

Parent, A. and Olivier, A. (1970) Comparative histochemical study of the corpus striatum. *J. Hirnforsch.* **12,** 73-81.

Parent, A., Descarries, L. and Beaudet, A. (1981) Organization of ascending serotonin systems in the adult rat brain. A radioautographic study after intraventricular administration of [^{3}H]5-hydroxytryptamine. *Neuroscience* **6,** 115-138.

Penny, G.R., Wilson, C.J. and Kitai, S.T. (1984) The influence of neostriatal patch and matrix compartments on the dendritic geometry of spiny projection neurons in the rat as revealed by intracellular labeling with HRP combined with immunocytochemistry. *Neurosci. Abstr.* **10,** 514.

Penny, G.R., Afsharpour, S. and Kitai, S.T. (1986) The glutamate decarboxylase-, leucine enkephalin-, methionine enkephalin- and substance P-immunoreactive neurons in the neostriatum of the rat and cat: evidence for partial population overlap . *Neuroscience* **17,** 1011-1045.

Percheron, G., Yelnik, J. and Francois, C. (1984) A Golgi analysis of the primate globus pallidus. III. Spatial organization of the striatopallidal complex. *J. Comp. Neurol.* **227,** 214-227.

Pert, C.B., Kuhar, M.J. and Snyder, S.H. (1976) Opiate receptors: autoradiographic localization in rat brain. *Proc. Natl. Acad. Sci.* **73,** 3729-3733.

Phillipson, O.T. and Griffiths, A.C. (1985) The topographic order of inputs to nucleus accumbens in the rat. *Neuroscience* **16,** 275-296.

Pijnenburg, A.J.J. and van Rossum, J.M. (1973) Stimulation of locomotor activity following injection of dopamine into the nucleus accumbens. *J. Pharm. Pharmacol.* **25,** 1003-1005.

Pilcher, W.H. and Joseph, S.A. (1984) Co-localization of CRF-ir perikarya and ACTH-ir fibers in rat brain. *Brain Res.* **299,** 91-102.

Porter, J.D., Guthrie, B.L. and Sparks, D.L. (1985) Selective retrograde transneuronal transport of wheat germ agglutinin-conjugated horseradish peroxidase in the oculomotor system. *Exp. Brain Res.* **57,** 411-416.

Powell, T.P.S. (1952) Residual neurons in the human thalamus following hemidecortication. *Brain* **75,** 571-583.

Powell, T.P.S. and Cowan, W.M. (1954) The connexions of the midline and intralaminar nuclei of the thalamus of the rat. *J. Anat.* **88,** 307-319.

Powell, T.P.S. and Cowan, W.M. (1956) A study of thalamo-striate relations in the monkey. *Brain* **79,** 364-390.

Powell, T.P.S. and Cowan, W.M. (1967) The interpretation of the degenerative changes in the intralaminar nuclei of the thalamus. *J. Neurol. Neurosurg. Psychiat.* **30,** 140-153.

Preuss, T.M. and Goldman-Rakic, P.S. (1987) Crossed corticothalamic and thalamocortical connections of macaque prefrontal cortex. *J. Comp. Neurol.* **257,** 269-281.

Price, J.L. (1981a) Towards a consistent terminology for the amygdaloid complex. In *The Amygdaloid Complex,* (Edited by Y. Ben-Ari) pp. 13-18. Elsevier, Amsterdam.

Price, J.L. (1981b) The efferent projections of the amygdaloid complex in the rat, cat and monkey. In *The Amygdaloid Complex,* (Edited by Y. Ben-Ari) pp. 121-132. Elsevier, Amsterdam.

Price, J.L. and Amaral, D.G. (1981) An autoradiographic study of the projections of the central nucleus of the monkey amygdala. *J. Neurosci.* **1,** 1242-1259.

Putnam, T. J. (1933) Treatment of athetosis and dystonia by section of extrapyramidal motor tracts. *Arch. Neurol. Psychiat.(Chicago)* **29,** 504-521.

Putnam, T. J. (1938) Results of treatment of athetosis by section of extrapyramidal tracts in the spinal cord. *Arch. Neurol. Psychiat.(Chicago)* **39,** 258-275.

Putnam, T. J. (1940) Treatment of unilateral paralysis agitans by section of the lateral pyramidal tract. *Arch. Neurol. Psychiat.(Chicago)* **44,** 950-976.

Rafal, R.D., Posner, M.I., Walker, J.A. and Friedrich, F.J. (1984) Cognition and the basal ganglia. Separating mental and motor components of performance in Parkinson's disease. *Brain* **107,** 1083-1094.

Ragsdale, C.W. and Graybiel, A.M. (1979) Striosomal organization of the caudate nucleus: III. Distribution of afferents from the frontal cortex of the cat. *Neurosci. Abstr.* **5,** 78.

Ragsdale, C.W. and Graybiel, A.M. (1981) The fronto-striatal projection in the cat and monkey and its relationship to inhomogeneities established by acetylcholinesterase histochemistry. *Brain Res.* **208,** 259-266.

Ragsdale, C.W. and Graybiel, A.M. (1983) Butyrylcholinesterase in the dorsal and ventral striatum: observations on histochemical distributions in adult, fetal and neonatal cats. *Neurosci. Abstr.* **9,** 15.

Ragsdale, C.W. and Graybiel, A.M. (1984) Further observations on the striosomal organization of frontostriatal projections in cats and monkeys. *Neurosci. Abstr.* **10,** 514.

Ragsdale, C.W. and Graybiel, A.M. (1987) Description of histochemical compartmentation in the cat's ventral striatum. Unpublished manuscript.

Raisman, G., Cowan, W.M. and Powell, T.P.S. (1966) An experimental analysis of the efferent projections of the hippocampus. *Brain* **89,** 83-108.

Reale, R.A. and Imig, T.J. (1980) Tonotopic organization in auditory cortex of the cat. *J. Comp. Neurol.* **192,** 265-291.

Reale, R.A. and Imig, T.J. (1983) Auditory cortical field projections to the basal ganglia of the cat . *Neuroscience* **8,** 67-86.

Rhodes, K.J., Joyce, J.N., Sapp. D.W. and Marshall, J.F. (1987) [^{3}H]Hemicholinium-3 binding in rabbit striatum: correspondence with patchy acetylcholinesterase staining and a method for quantifying striatal compartments. *Brain Res.* **412,** 400-404.

Ricardo, J.A. and Koh, E.T. (1978) Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. *Brain Res.* **153,** 1-26.

Rinvik, E. (1984) Thalamic commissural connections in the cat. *Neurosci. Lett.* **44,** 311-316.

Robertson, R.T. and Feiner, A.R. (1982) Diencephalic projections from the pontine reticular formation: autoradiographic studies in the cat. *Brain Res.* **239,** 3-16.

Rockland, K.S. and Pandya, D.N. (1979) Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. *Brain Res.* **179,** 3-20.

Rolls, E.T. (1983) The initiation of movements. *Exp. Brain Res. Suppl.* **7,** 97-113.

Rolls, E.T., Thorpe, S.J. and Maddison, S.P. (1983) Responses striatal neurons in the behaving monkey. I. Head of the caudate nucleus. *Behav. Brain Res.* **7,** 179-210.

Rolls, E.T., Thorpe, S.J., Boytim, M., Szabo, I. and Perrett, D.T. (1984) Responses of striatal neurons in the behaving monkey. III. Effects of iontophoretically applied dopamine on normal responsiveness. *Neuroscience* **12,** 1201-1212.

Room, P., Russchen, F.T., Groenewegen, H.J. and Lohman, A.H.M. (1985) Efferent connections of the prelimbic (area 32) and the infralimbic (area 25) cortices: an anterograde tracing study in the cat. *J. Comp. Neurol.* **242,** 40-55.

Rose, J.E. (1942) The thalamus of the sheep: cellular and fibrous structure and comparison with pig, rabbit and cat. *J. Comp. Neurol.* **77,** 469-523.

Rose, J.E. (1949) The cellular structure of the auditory area of the cat. *J. Comp. Neurol.* **91,** 409-439.

Rose, J.E. and Woolsey, C.N. (1943) A study of thalamocortical relations in the rabbit. *Bull. Johns Hopkins Hosp.* **73,** 65-128.

Rose, J.E. and Woolsey, C.N. (1948a) Structure and relations of limbic cortex and anterior thalamic nuclei in rabbit and cat. *J. Comp. Neurol.* **89,** 279-340.

Rose, J.E. and Woolsey, C.N. (1948b) The orbitofrontal cortex and its connections with the mediodorsal nucleus in rabbit, sheep, and cat. In *Research Publications for Nervous and Mental Disease Vol. 27 The Frontal Lobes* (Edited by J.F. Fulton, C.D. Aring and S.B. Wortis) pp. 210-232. Williams and Wilkins, Baltimore.

Rose, J.E. and Woolsey, C.N. (1958) Cortical connections and functional organization of the thalamic auditory system of the cat. In *Biological and Biochemical Bases of Behavior*, (Edited by Harlow, H.F. and Woolsey, C.N.) pp. 127-150. University of Wisconsin, Madison.

Rosene, D.L. and Van Hoesen, G.W. (1977) Hippocampal efferents reach widespread areas of cerebral cortex and amygdala in the rhesus monkey. *Science* **198,** 315-317.

Rosvold, H.E. (1968) The prefrontal cortex and caudate nucleus: a system for effecting correction in response mechanisms. In *Mind as a Tissue*, (Edited by C. Rupp) pp. 21-38. Harper and Row, New York.

Rosvold, H.E. and Delgado, J.M.R. (1956) The effect on delayed-alternation test performance of stimulating or destroying electrically structures within the frontal lobes of the monkey's brain. *J. Comp. Physiol. Psychol.* **49,** 365-372.

Rosvold, H.E., Mishkin, M. and Szwarcbart, M.K. (1964) Neural substrates unsolved in delayed response performance. In *The Frontal Granular Cortex and Behavior*, (Edited by J.M. Warren and K. Akert) pp. 1-15. McGraw-Hill, New York.

Rosvold, H.E., Mishkin, M. and Szwarcbart, M.K. (1958) Effects of subcortical lesions in monkeys on visual-discrimination and single-alternation performance. *J. Comp. Physiol. Psychol.* **51,** 437-444.

Royce, G.J. (1978a) Autoradiographic evidence for a discontinuous projection to the caudate nucleus from the centromedian nucleus in the cat. *Brain Res.* **146,** 145-150.

Royce, G.J. (1978b) Cells of origin of subcortical afferents to the caudate nucleus: a horseradish peroxidase study in the cat. *Brain Res.* **153,** 465-475.

Royce, G.J. (1982) Laminar origin of cortical neurons which project upon the caudate nucleus: a horseradish peroxidase study in the cat. *J. Comp. Neurol.* **205,** 8-29.

Royce, G.J. (1983) Single thalamic neurons which project to both the rostral cortex and caudate nucleus studied with the fluorescent double labeling method. *Exp. Neurol.* **79,** 773-784.

Royce, G.J. and Mourey, R.J. (1985) Efferent connections of the centromedian and parafascicular thalamic nuclei: an autoradiographic investigation in the cat. *J. Comp. Neurol.* **235,** 277-300.

Russchen, F.T. (1981) *Afferent connections of the amygdaloid complex in the cat.* Doctoral dissertation, Vrije Universiteit te Amsterdam, Amsterdam, The Netherlands.

Russchen, F.T. (1982a) Amygdalopetal projections in the cat. I. Cortical afferent connections. A study with retrograde and anterograde tracing techniques. *J. Comp. Neurol.* **206,** 159-179.

Russchen, F.T. (1982b) Amygdalopetal projections in the cat. II. Subcortical afferent connections. A study with retrograde tracing techniques. *J. Comp. Neurol.* **207,** 157-176.

Russchen, F.T. and Price, J.L. (1984) Amygdalostriatal projections in the rat. Topographical organization and fiber morphology shown using the lectin PHA-L as an anterograde tracer. *Neurosci. Lett.* **47,** 15-22.

Russchen, F.T., Bakst, I., Amaral, D.G. and Price, J.L. (1985) The amygdalostriatal projections in the monkey. An anterograde tracing study. *Brain Res.* **329,** 241-257.

Rye, D.B., Saper, C.B. and Wainer, B.H. (1984) Stabilization of the tetramethylbenzidine (TMB) reaction product: application for retrograde and anterograde tracing, and combination with immunohistochemistry. *J. Histochem. Cytochem.* **32,** 1145-1153.

Sandell, J.H., Graybiel, A.M. and Chesselet, M.F. (1986) A new enzyme marker for striatal compartmentalization: NADPH diaphorase activity in the caudate nucleus and putamen of the cat. *J. Comp. Neurol.* **243,** 326-334.

Sanides, F. (1970) Functional architecture of motor and sensory cortices in primates in light of a new concept of neocortex evolution. In *The Primate Brain,* (Edited by C.R. Noback and W. Montagna) pp. 137-208. Appleton-Century-Crofts Educational Division, New York.

Saper, C.B. and Loewy, A.F. (1980) Efferent connections of the parabrachial nucleus in the rat. *Brain Res.* **197,** 291-318.

Saper, C.B., Swanson, L.W. and Cowan, W.M. (1976) The efferent connections of the ventromedial nucleus of the hypothalamus of the rat. *J. Comp. Neurol.* **169,** 409-442.

Saper, C.B., Swanson, L.W. and Cowan, W.M. (1978) The efferent connections of the anterior hypothalamic area of the rat, cat and monkey. *J. Comp. Neurol.* **182,** 575-600.

Saper, C.B., Swanson, L.W. and Cowan, W.M. (1979a) An autoradiographic study of the efferent connections of the lateral hypothalamic area in the rat. *J. Comp. Neurol.* **183,** 689-706.

Saper, C.B., Swanson, L.W. and Cowan, W.M. (1979b) Some efferent connections of the rostral hypothalamus in the squirrel monkey (*Saimiri sciureus*) and cat. *J. Comp. Neurol.* **184,** 205-242.

Sato, M., Itoh, K. and Mizuno, N. (1979) Distribution of thalamo-caudate neurons in the cat as demonstrated by horseradish peroxidase. *Exp. Brain Res.* **34,** 143-153.

Scheibel, M.E. and Scheibel, A.B. (1967) Structural organization of nonspecific thalamic nuclei and their projection towards cortex. *Brain Res.* **6,** 60-84.

Schell, G.R. and Strick, P.L. (1984) The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. *J. Neurosci.* **4,** 539-560.

Schlag, J. and Schlag-Rey, M. (1970) Induction of oculomotor responses by electrical stimulation of the prefrontal cortex in the cat. *Brain Res.* **22,** 1-13.

Schlag, J. and Schlag-Rey, M. (1987) Evidence for a supplementary eye field. *J. Neurophysiol.* **57,** 179-200.

Schultz, W. (1986) Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey. *J. Neurophysiol.* **56,** 1439-1461.

Schultz, W. and Romo, R. (1986) Dopamine neurons of the monkey midbrain discharge in response to sensory stimuli implicated in behavioral reactions. *Neurosci. Abstr.* **12,** 207.

Selemon, L.D. and Goldman-Rakic, P.S. (1985) Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *J. Neurosci.* **5,** 776-794.

Seltzer, B. and Van Hoesen, G.W. (1979) A direct inferior parietal lobule projection to the presubiculum in the rhesus monkey. *Brain Res.* **179,** 157-161.

Sherk, H. (1986) Location and connections of visual cortical areas in the cat's suprasylvian sulcus. *J. Comp. Neurol.* **247,** 1-31.

Shipley, M.T. (1975) The topographic and laminar organization of the presubiculum's projection to the ipsi- and contralateral entorhinal cortex in the guinea pig. *J. Comp. Neurol.* **160,** 127-146.

Shute, C.C.D. and Lewis, P.R. (1963) Cholinesterase-containing systems of the brain of the rat. *Nature* **199,** 1160-1164.

Sims, K.L., Kauffman, F.C., Johnson, E.C. and Pickel, V.M. (1974) Cytochemical localization of brain nicotinamide adenine dinucleotide phosphate (oxidized)-dependent dehydrogenases. *J. Histochem. Cytochem.* **22,** 7-19.

Spiegler, B.J. and Mishkin, M. (1981) Evidence for the sequential participation of inferior temporal cortex and amygdala in the acquisition of stimulus reward associations. *Behav. Brain Res.* **3,** 303-317.

Squatrito, S., Maioli, M.G., Galletti, C. and Battaglini, P.P. (1981) Basal ganglia projections from visual cortical areas in the *Macaca fascicularis*. *Neurosci. Lett. Suppl.* **7,** S148.

Squire, L.R. (1981) Two forms of human amnesia: an analysis of forgetting. *J. Neurosci.* **1,** 635-640.

Standaert, D.G., Needleman, P. and Saper, C.B. (1986) Organization of atriopeptin-like immunoreactive neurons in the central nervous system of the rat. *J. Comp. Neurol.* **253,** 315-341.

Steinbusch, H.W.M. (1982) Distribution of serotonin-immunoreactivity in the central nervous system of the rat- cell bodies and terminals. *Neuroscience* **6,** 557-618.

Sternberger, L.A. (1979) *Immunocytochemistry.* Wiley, New York.

Strecker, R.E., Steinfels, G.F., Abercrombie, E.D. and Jacobs, B.L. (1985) Caudate unit activity in freely moving cats: effects of phasic auditory and visual stimuli. *Brain Res.* **329,** 350-353.

Streit, P. (1980) Selective retrograde labeling indicating the transmitter of neuronal pathways. *J. Comp. Neurol.* **191,** 429-463.

Sugimoto, T. and Hattori, T. (1984) Direct projections from the globus pallidus to the paraventricular nucleus of the thalamus in the rat. *Brain Res.* **323,** 188-192.

Sugimoto, T., Mizuno, N. and Itoh, K. (1981) An autoradiographic study on the terminal distribution of cerebellothalamic fibers in the cat. *Brain Res.* **215,** 29-47.

Sugimoto, T., Takada M., Kaneko, T. and Mizuno, N. (1987) Neurotensin in projection neurons of the striatum and nucleus accumbens, with reference to coexistence with enkephalin and GABA: an immunohistochemical study in the cat. *J. Comp. Neurol.* **257,** 383-395.

Swanson, L.W. (1976) An autoradiographic study of the efferent connections of the preoptic area in the rat. *J. Comp. Neurol.* **167,** 227-256.

Swanson, L.W. (1981) A direct projection from Ammon's horn to prefrontal cortex in the rat. *Brain Res.* **217,** 150-154.

Swanson, L.W. and Cowan, W.M. (1975) A note on the connections and development of the nucleus accumbens. *Brain Res.* **92,** 324-330.

Swanson, L.W. and Hartman, B.K. (1975) The central adrenergic system: an immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-β-hydroxylase as a marker. *J. Comp. Neurol.* **163,** 467-506.

Swanson, L.W. and Kohler, C. (1986) Anatomical evidence for direct projections from the entorhinal area to the entire cortical mantle in the rat. *J. Neurosci.* **6,** 3010-3023.

Swanson, L.W., Mogenson, G.J., Gerfen, C.R. and Robinson, P. (1984) Evidence for a projection from the lateral preoptic area and substantia innominata to the 'mesencephalic locomotor region' in the rat. *Brain Res.* **295,** 161-178.

Switzer, R.C. III, Hill, J. and Heimer, L. (1982) The globus pallidus and its rostroventral extension into the olfactory tubercle of the rat: a cyto- and chemoarchitectural study. *Neuroscience* **7,** 1891-1904.

Takada, M., Itoh, K., Yasui, Y., Sugimoto, T. and Mizuno, N. (1984) Direct projections from the substantia nigra to the posterior thalamic regions in the cat. *Brain Res.* **309,** 143-146.

Takada, M., Itoh, K., Yasui, Y., Sugimoto, T. and Mizuno, N. (1985a) Topographical projections from the posterior thalamic regions to the striatum in the cat, with reference to possible tecto-thalamo-striatal connections. *Exp. Brain Res.* **60,** 385-396.

Takada, M., Itoh, K., Sugimoto, T. and Mizuno, N. (1985b) Topographical projections from the thalamus to the putamen in the cat. *Neurosci. Lett.* **54,** 207-212.

Takada, M., Fishell, G., Li, Z.K., van der Kooy, D. and Hattori, T. (1987) The development of laterality in the forebrain projections of midline thalamic cell groups in the rat. *Dev. Brain Res.* **35,** 275-282.

Tanaka, D. (1987) Differential laminar distribution of corticostriatal neurons in the prefrontal and pericruciate gyri of the dog. *J. Neurosci.* **7,** 4095-4106.

Tanaka, D., Isaacson, L.G. and Trosko, B.K. (1986) Thalamostriatal projections from the ventral anterior nucleus in the dog. *J. Comp. Neurol.* **247,** 56-68.

Tanji, D.G., Wise, S.P., Dykes, R.W. and Jones, E.G. (1978) Cytoarchitecture and thalamic connectivity of third somatosensory area of cat cerebral cotex. *J. Neurophysiol.* **41,** 268-284.

Teuber, H.-L. (1976) Complex functions of basal ganglia. In *Res. Publ. Assoc. Res. Nerv. Ment. Dis. Vol. 55 The Basal Ganglia* (Edited by M.D. Yahr) pp. 151-169. Raven Press, New York.

Turner, B. and Herkenham, M. (1981) An autoradiographic study of thalamo-amygdaloid connections in the rat. *Anat. Rec.* **199,** 260A.

Tusa, R.J. and Palmer, L.A. (1980) Retinotopic organization of areas 20 and 21 in the cat. *J. Comp. Neurol.* **193,** 147-164.

Tusa, R.J., Rosenquist, A.C. and Palmer, L.A. (1979) Retinotopic organization of areas 18 and 19 in the cat. *J. Comp. Neurol.* **185,** 657-678.

Tusa, R.J., Palmer, L.A. and Rosenquist, A.C. (1981) Multiple cortical visual areas: visual field topography in the cat. In *Cortical Sensory Organization Vol. 2 Multiple Visual Areas* (Edited by C.N. Woolsey) pp. 1-32. Humana Press, Clifton, NJ.

Updyke, B.V. (1986) Retinotopic organization within the cat's posterior suprasylvian sulcus and gyrus. *J. Comp. Neurol.* **246,** 265-280.

Valenstein, E.S. and Nauta, W.J.H. (1959) A comparison of the distribution of the fornix system in the rat, guinea pig, cat, and monkey. *J. Comp. Neurol.* **113,** 337-363.

van der Kooy, D. (1979) The organization of the thalamic, nigral and raphe cells projecting to the medial vs. lateral caudate-putamen in rat. A fluorescent retrograde double labeling technique. *Brain Res.* **169,** 381-387.

van der Kooy, D. and Fishell, G. (1987) Neuronal birthdate underlies the development of striatal compartments. *Brain Res.* **401,** 155-161.

van der Kooy, D. and Kolb, B. (1985) Non-cholinergic globus pallidus cells that project to the cortex but not to the subthalamic nucleus in rat. *Neurosci. Lett.* **57,** 113-118.

Van Essen, D. (1985) Functional organization of primate visual cortex. In *Cerebral Cortex Vol. 3* (Edited by A. Peters and E.G. Jones) pp. 259-329. Plenum Press, New York.

Van Hoesen, G.W. and Pandya, D.N. (1975) Some connections of the entorhinal (area 28) and perirhinal (area 35) cortices of the rhesus monkey. I. Temporal lobe afferents. *Brain Res.* **95,** 1-24.

Van Hoesen, G.W., Yeterian, E.H. and Lavizzo-Mourey, R. (1981) Widespread corticostriate projections from temporal cortex of the rhesus monkey. *J. Comp. Neurol.* **199,** 205-219.

Veening, J.G., Cornelissen, F.M. and Lieven, P.A.J.M. (1980) The topical organization of afferents to the caudatoputamen of the rat. A horseradish peroxidase study. *Neuroscience* **5,** 1253-1268.

Vertes, R.P., Martin, G.F. and Waltzer, R. (1986) An autoradiographic analysis of ascending projections from the medullary reticualr formation in the rat. *Neuroscience* **19,** 873-898.

Villablanca, J.R., Marcus, R.J. and Olmstead, C.E. (1976) Effects of caudate nuclei or frontal cortex ablations in cats. I. Neurology and gross behavior. *Exp. Neurol.* **52,** 389-420.

Vogt, C. (1911) Quelques considerations generales a propos du syndrome du corps strie. *J. Psychol. Neurol.(Lpz.)* **18,** 479-488.cited in Wilson (1912).

Vogt, B.A., Pandya, D.N. and Rosene, D.L. (1987) Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents. *J. Comp. Neurol.* **262,** 256-270.

Walker, A.E. (1938) *The Primate Thalamus.* Univ. of Chicago Press, Chicago.

Waller, W.H. (1934) Topographical relations of cortical lesions to thalamic nuclei in the albino rat. *J. Comp. Neurol.* **60,** 237-269.

Waters, C.M., Hunt, S.P., Jenner, P. and Marsden, C.D. (1987) Localization of neurotensin receptors in the forebrain of the common marmoset and the effects of treatment with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Brain Res.* **412,** 244-253.

Webster, K.E. (1961) Cortico-striate interrelations in the albino rat. *J.Anat.* **95,** 532-544.

Webster, K.E. (1965) The cortico-striatal projection in the cat. *J.Anat.* **99,** 329-337.

Weinrich, M. and Wise, S.P. (1982) The premotor cortex of the monkey. *J. Neurosci.* **2,** 1329-1345.

Weiskrantz, L. (1956) Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *J. Comp. Physiol. Psychol.* **49,** 381-391.

Whittier, J.R. and Mettler, F.A. (1949) Studies on the subthalamus of the rhesus monkey. II. Hyperkinesia and other pysiologic effects of subthalamic lesions, with special reference to the subthalamic nucleus of Luys. *J. Comp. Neurol.* **90,** 319-372.

Wiegand, S.J. and Price, J.L. (1982) Thalamocortical projections to the lateral prefrontal cortex and adjacent cortical areas in rats and cats. *Neurosci. Abstr.* **8,** 211.

Wilson, S.A.K. (1912) Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. *Brain* **34,** 295-488.

Wilson, S.A.K. (1914) An experimental research into the anatomy and physiology of the corpus striatum. *Brain* **36,** 427-492.

Wilson, S.A.K. (1925) Disorders of motility and muscle tone with special reference to the corpus striatum. The Croonian Lectures. Lecture IV. Athetosis. *Lancet ii,* 215-291.

Wise, S.P. and Jones, E.G. (1977) Cells of origin and terminal distribution of descending projections of the rat somatic sensory cortex. *J. Comp. Neurol.* **175,** 129-158.

Wong, D.F., Wagner, H.N.., Tune, L.E., Dannals, R.F., Pearlson, G.D., Links, J.M., Tamminga, C.A., Broussolle, E.P., Ravert, H.T., Wilson, A.A., Toung, J.K.T., Malat, J., Williams, J.A., O'Tuama, L.A., Snyder, S.H., Kuhar, M.J. and Gjedde, A.J. (1986) Positron emission tomography reveals elevated D_2 dopamine receptors in drug-naive schizophrenics. *Science* **234,** 1558-1563.

Woolsey, C.N. (1959) Organization of cortical auditory system. In *Sensory Communication,* (Edited by Rosenblith, W.A.) pp. 235-257. M.I.T. Press/J. Wiley & Sons,

Wright, A.K. and Arbuthnott, G.W. (1981) The pattern of innervation of the corpus striatum by the substantia nigra. *Neuroscience* **6,** 2063-2067.

Wurtz, R.H. and Albano, J.E. (1980) Visual-motor function of the primate superior colliculus. In *Annual Review of Neuroscience Vol. 3* (Edited by W.M. Cowan, Z.W. Hall and E.R. Kandel) pp. 189-226. Annual Reviews, Palo Alto, CA.

Wyss, J.M., Swanson, L.W. and Cowan, W.M. (1979) A study of subcortical afferents to the hippocampal formation in the rat. *Neuroscience* **4,** 463-476.

Yahr, M.D. (Editor) (1976) *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* . Vol. 55 *The Basal Ganglia.* Raven Press, New York.

Yakovlev, P.I. (1959) Pathoarchitectonic studies of cerebral malformations. III. Arhinencephalies (Holotelencephalies). *J. Neuropath. Exp. Neurol.* **18,** 22-25.

Yasui, Y., Itoh, K., Sugimoto, T., Kaneko, T. and Mizuno, N. (1987) Thalamocortical and thalamo-amygdaloid projections from the parvicellular division of the posteromedial ventral nucleus in the cat. *J. Comp. Neurol.* **257,** 253-268.

Yeterian, E.H. and Van Hoesen, G.W. (1978) Cortico-striate projections in the rhesus monkey: the organization of certain cortico-caudate connections. *Brain Res.* **139,** 43-63.

Young, W.S., Alheid, G.F. and Heimer, L. (1984) The ventral pallidal projection to the mediodorsal thalamus: a study with fluorescent retrograde tracers and immunohistofluorescence. *J. Neurosci.* **4,** 1626-1638.

Yumiya, H. and Ghez, C. (1984) Specialized subregions in the cat motor cortex: anatomical demonstration of differential projections to rostral and caudal sectors. *Exp. Brain Res.* **53,** 259-276.

Zaborszky, L., Eckenstein, F., Leranth, C., Oertel, W., Schmechel, P., Alones, V. and Heimer, L. (1984) Cholinergic cells of the ventral pallidum: a combined electron microscopic immunocytochemical, degeneration and HRP study. *Neurosci. Abstr.* **10,** 8.

Zemlan, F.P., Behbehani, M.M. and Beckstead, R.M. (1984) Ascending and descending projections from nucleus reticularis magnocellularis and nucleus reticularis gigantocellularis: an autoradiographic and horseradish peroxidase study in the rat. *Brain Res.* **292,** 207-220.