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An Experimental Study of the Ventral Striatum of the Golden Hamster. II. Neuronal Connections of the Olfactory Tubercle

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ABSTRACT As part of an experimental study of the ventral striatum, the horseradish peroxidase (HRP) method was used to examine the afferent and efferent neuronal connections of the olfactory tubercle. Following iontophoretic applications or hydraulic injections of HRP in the tubercle, neurons labeled by retrograde transport of HRP were observed ipsilaterally in the telencephalon in the main olfactory bulb, the medial, lateral, ventral, and posterior divisions of the anterior olfactory nucleus, and in the orbital, ventral, and posterior agranular insular, primary olfactory, perirhinal, and entorhinal cortices. Labeled cells were also present in the basolateral, basomedial, anterior cortical, and posterolateral cortical amygdaloid nuclei, and bilaterally in the nucleus of the lateral olfactory tract. In the diencephalon, ipsilateral HRP-containing neurons were observed in the midline nuclei paraventricularis, parataenialis, and reuniens, and in the parafascicular intralaminar nucleus. Retrograde labeling was present in the ipsilateral brainstem in cells of the ventral tegmental area, substantia nigra, and dorsal raphe. Many of the above projections to the tubercle were found to be topographically organized.

Anterograde axonal transport of HRP from the olfactory tubercle labeled terminal fields ipsilaterally in all parts of the anterior olfactory nucleus, in the ventral pallidum, and in the substantia nigra, pars reticulata. Contralaterally, terminal fields were present in the dorsal and lateral divisions of the anterior olfactory nucleus.

The projections to the tubercle from the orbital, ventral, and posterior agranular insular, and perirhinal neocortices, intralaminar thalamus, and dopamine-containing areas of the ventral mesencephalon are analogous to the connections of the caudatoputamen, as are the efferents from the tubercle to the ventral globus pallidus and substantia nigra. These connections substantiate the recent suggestion that the olfactory tubercle is a striatal structure, and provide support for the ventral striatal concept.

In the present study of the olfactory tubercle, and in the first study in this series on the nucleus accumbens, the ventral striatum was found to receive projections from a number of limbic system structures, including the main olfactory bulb, anterior olfactory nucleus, amygdala, hippocampus, and subiculum, and the entorhinal and primary olfactory cortices. These findings suggest that the ventral striatum is concerned with integrating limbic information into the striatal system.

The olfactory tubercle, because it receives input from the olfactory bulb, is generally considered to be an olfactory area. Recently, however, Heimer and Wilson ('75) have suggested that the tubercle is in fact a striatal structure. Citing embryological, cytological, histochemical, and hodological evidence, these investigators have proposed that the olfactory tubercle, the nucleus accumbens, and the substriatal gray are related striatal structures.

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Heimer and Wilson refer to these three areas and the cell bridges connecting them as the "ventral striatum," and have shown that nucleus accumbens and the olfactory tubercle project to a subcommissural rostroventral extension of the globus pallidus they have termed the "ventral pallidum." Thus, the ventral striatum and ventral pallidum may together constitute a ventral striato-pallidal system. In contrast to the neocortical input to the caudatoputamen, however, the known telencephalic inputs to the ventral striatum are primarily from limbic structures, including the olfactory cortex, hippocampus, and amygdala (Heimer and Wilson, '75). Thus, the ventral striatum is one of the few areas in which the limbic and striatal systems interact directly. In order to experimentally evaluate the ventral striatal hypothesis and to further define the anatomy of this area, the afferent and efferent connections of the olfactory tubercle, which have never been systematically studied with modern methods, were examined in the golden hamster using the method of axonal transport of the protein horseradish peroxidase (HRP). The results of experiments on the nucleus accumbens were presented in a previous paper (Newman and Winans, this issue); those pertaining to the tubercle are described here.

METHODS

The present study utilized the same group of 50 golden hamsters described in the first paper in this series (Newman and Winans, this issue). The experimental techniques employed in this study were also fully described in that paper. Briefly, in 20 animals HRP (Miles, 0.5 mg/μl in Tris buffer, pH 8.6) was iontophoretically deposited in the olfactory tubercle or neighboring forebrain structures using a glass micropipette (tip diameter 25–40 μm) and a Grass SD5 or S88 stimulator. In 30 animals, HRP (Sigma II or VI, or Miles; 0.1–0.5 mg/μl in 0.9% saline) was injected into the tubercle or surrounding areas with a Hamilton syringe and 26-gauge needle. In most cases, a direct approach to the tubercle was used, the pipette or needle being lowered vertically from the dorsal surface of the brain. In some iontophoretic experiments, the micropipette was directed into the tubercle at an angle from the contralateral side of the brain in order to avoid possible HRP contamination of cortical and striatal areas overlying the tubercle.

The animals were allowed to survive from 18–48 hours, then perfused with buffered saline followed by a fixative solution containing glutaraldehyde, and in some cases, paraformaldehyde as well. The brains were removed from the skulls, washed overnight in buffered sucrose solution, and cut coronally in 40 μm sections on a freezing microtome. Every fourth section was reacted for HRP using either diaminobenzidine (DAB), tetramethylbenzidine (TMB), o-dianisidine, or benzidine dihydrochloride (BDHC) as a reagent, then mounted on gelatin-coated slides. Sections adjacent to those reacted with DAB or BDHC were mounted and stained with cresyl violet, and sections reacted with TMB or dianisidine were counter-stained with safranin-o and cresyl violet, respectively. The reacted sections were examined microscopically under both brightfield and darkfield illumination.

RESULTS

Technical considerations

Factors influencing the size and characteristics of an HRP application site, the criteria by which the limits of an application site were defined, and the criteria by which retrograde neuronal and anterograde terminal labeling were identified, have been fully discussed in the first paper in this series (Newman and Winans, this issue) and will only be summarized here.

Three regions were observed within the application sites: 1) a dense central area in which a large amount of reaction product was present in neurons and in the extracellular space; 2) a middle zone in which there was only a moderate amount of extracellular material; and 3) a peripheral zone in which a small amount of HRP was present in neuron cell bodies only. In this study, it was assumed that transport of HRP could occur only from regions (1) and (2), since the concentration of HRP in region (3) was very low. Therefore, an application site was said to be restricted to a given cytoarchitectural area only if the central and middle regions did not extend beyond the boundaries of that area.

Neurons were said to be labeled by retrograde transport if they were outside the application site and contained discrete granular HRP reaction product in their cytoplasm. Terminal fields labeled by orthograde transport of HRP appeared as clouds of coarsely-granular reaction product distributed within the neuropil of a cytoarchitecturally defined area.

Experimental results

A number of the connections of the olfactory tubercle display topographical organization. In order that this may be demonstrated, two experiments in which HRP applications were made in different parts of the rostral olfactory tubercle will be presented in detail, and the results of several additional experiments which help illustrate topographical relationships will be summarized.

Rostromedial olfactory tubercle

In experiment 791, an iontophoretic application of HRP was made in the medial third of the rostral olfactory tubercle (Figs. 1A; 2C,D).

Retrograde transport of HRP produced labeled neurons in a number of ipsilateral telencephalic areas in this brain. The main olfactory bulb (MOB) was very lightly labeled, as were the lateral, medial, and ventral subdivisions of the anterior olfactory nucleus (AON) (Fig. 2A,B).

In the cerebral cortex, HRP-containing pyramidal cells were present along the rhinal sulcus in the ventrolateral orbital cortex (terminology of Krettek and Price, '77a) (Fig. 2A), the ventral and posterior agranular insular cortices (of Krettek and Price, '77a; Figs. 2B–K; 4), and perirhinal cortex (Fig. 2L–O). Pyramidal cells containing reaction product were also observed in the primary olfactory cortex throughout its rostral-caudal extent, though these cells were most numerous caudal to the level of the nucleus of the lateral olfactory tract (NLOT) (Figs. 2H–K; 4). Rostral to this level, labeling was mostly confined to cells in lamina II of the cortex, while caudally, labeled neurons were found in lamina III as well. The superficial and deep laminae of entorhinal areas 28L, 28L', and TR (of Haug, '76) also contained many labeled neurons (Figs. 2L–O; 6).

Retrogradely transported HRP appeared in a number of nuclei of the amygdaloid complex. Many cells in both the anterior and posterior divisions of the basolateral nucleus (of Krettek and Price, '78b) were filled with granular reaction product (Figs. 2I–L; 5), as were those of the anterior and posterolateral cortical nuclei (Fig. 2I–K). Smaller numbers of HRP-containing cells were present in the basomedial nucleus, and bilaterally in the NLOT.

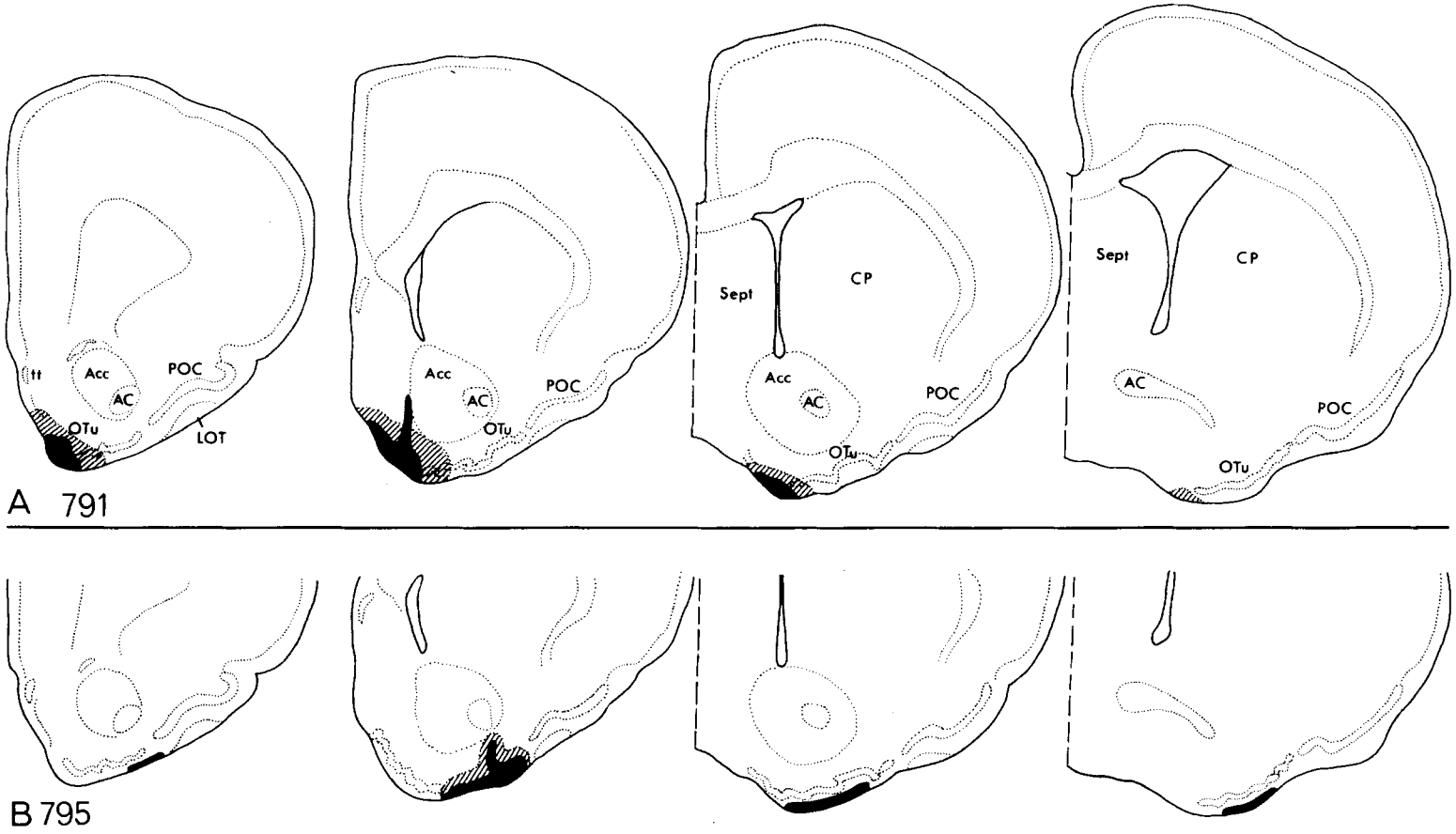
Ipsilaterally-labeled thalamic nuclei included parataenialis (Fig. 2H–J) and parafascicularis, which were heavily labeled, as well as paraventricularis (Fig. 2G–I) and reuniens (Fig. 2H). Horseradish peroxidase-containing neurons were observed in parafascicularis only in the rostral portion of the nucleus, medial to the fasciculus retroflexus (Fig. 2J).

In the ipsilateral brainstem, many large, labeled multipolar were observed in the ventral tegmental area (Fig. 2M,N). These neurons were rostrally continuous with similar labeled cells in the area medial to Forel's field H2. Horseradish peroxidase was also present in neurons in the caudal mesencephalic portion of the dorsal raphe (Fig. 2–O).

Terminal fields were observed in a number of areas in this experiment. A dense terminal field was observed in laminae 1A and 1B in all parts (dorsal, ventral, medial, lateral, and

Abbreviations

AC	anterior commissure
Acc	nucleus accumbens
AIV	ventral agranular insular cortex
Bla	basolateral amygdaloid nucleus, anterior division
Blp	basolateral amygdaloid nucleus, posterior division
C1	anterior cortical amygdaloid nucleus
C2	posterolateral cortical amygdaloid nucleus
C3	posteromedial cortical amygdaloid nucleus
Ce	central amygdaloid nucleus
CP	caudatoputamen
d	anterior olfactory nucleus, pars dorsalis
DR	dorsal raphe
FR	fasciculus retroflexus
GP	globus pallidus
H2	Forel's field H2
IPN	interpeduncular nucleus
l	anterior olfactory nucleus, pars lateralis
L	lateral amygdaloid nucleus
LOT	lateral olfactory tract
m	anterior olfactory nucleus, pars medialis
M	medial amygdaloid nucleus
NLOT	nucleus of the lateral olfactory tract
OTu	olfactory tubercle
PF	parafascicular thalamic nucleus
PIC	posterior agranular insular cortex
POC	primary olfactory cortex
PR	perirhinal cortex
PT	parataenial thalamic nucleus
PV	paraventricular thalamic nucleus
RE	thalamic nucleus reuniens
RS	rhinal sulcus
Sept	septum
SN	substantia nigra
TR	entorhinal cortical area TR
tt	taenia tecta
v	anterior olfactory nucleus, pars ventralis
VP	ventral pallidum
VTA	ventral tegmental area
28L	entorhinal cortical area 28L
28L'	entorhinal cortical area 28L'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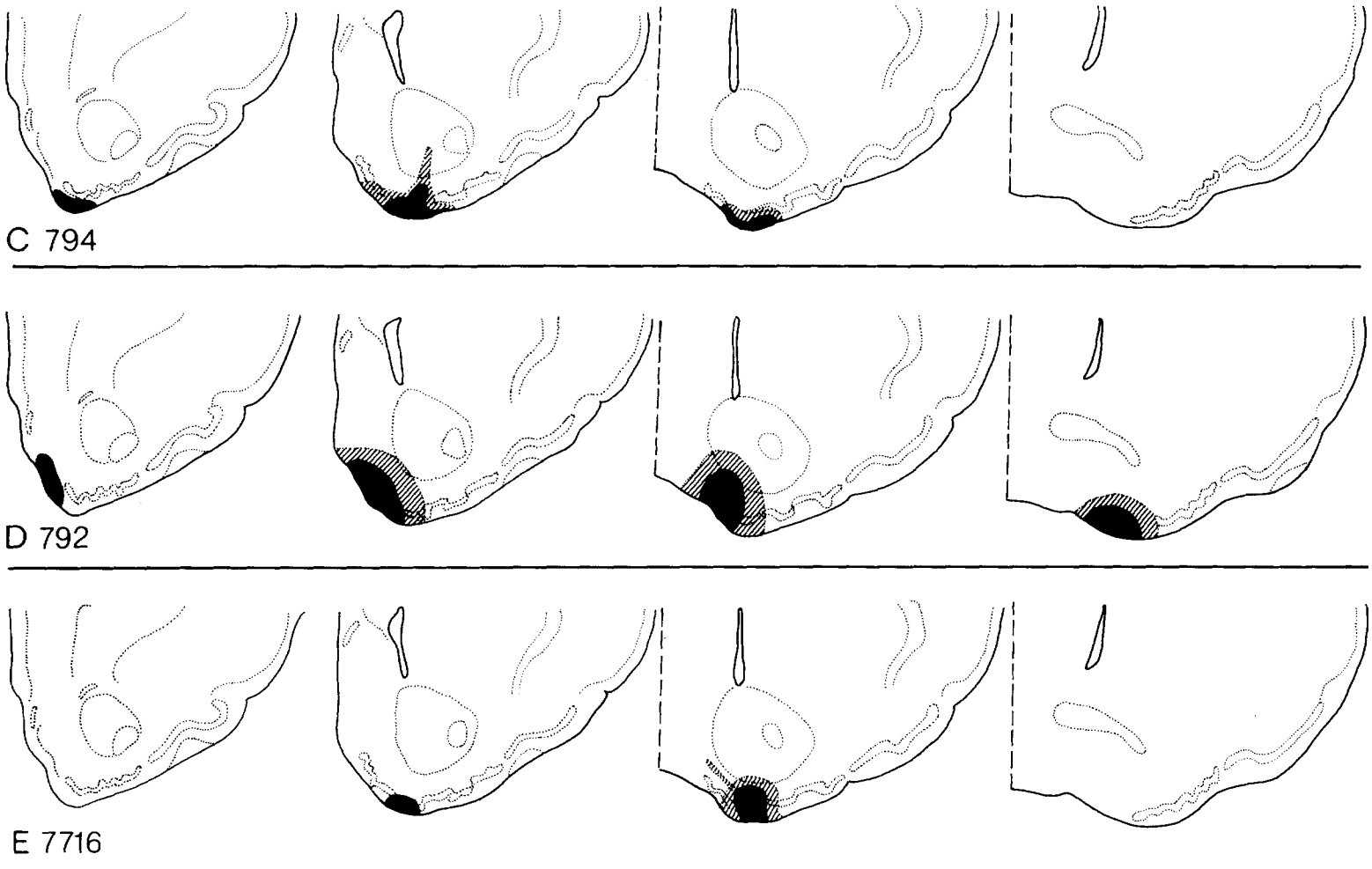
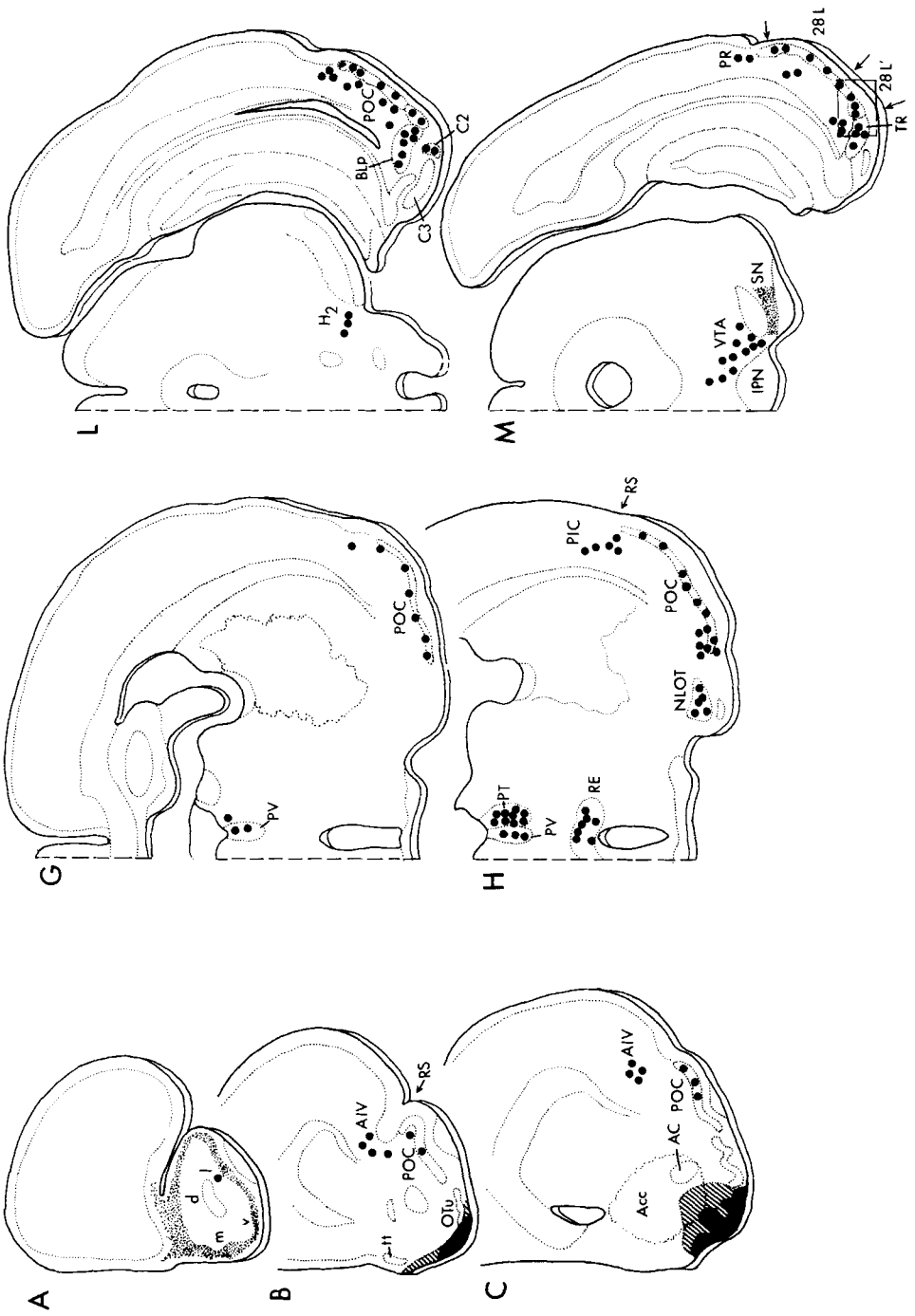


Fig. 1. Five series of drawings of representative coronal sections depicting in detail the HRP application site in each of the brains discussed in the text. In this figure, and in Figures 2 and 3, the solid-shaded areas represent zones 1 and 2 of the application sites, as described in the text, while the diagonal shading represents zone 3.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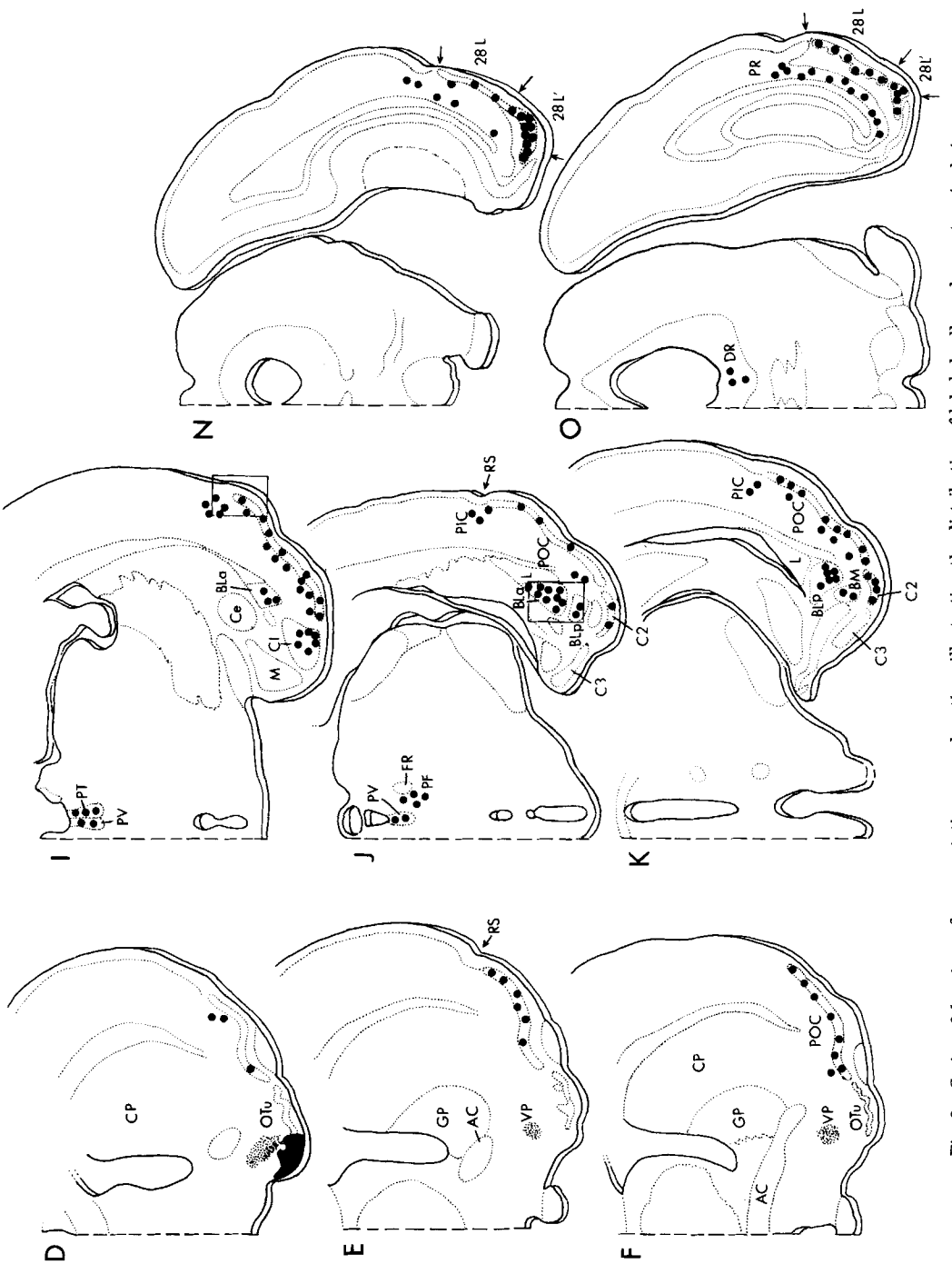


Fig. 2. Series of drawings of representative coronal sections illustrating the distribution of labeled cells and axon terminals in brain 791. In this figure, and in Figure 3, labeled neurons are indicated by solid circles, and labeled terminals by stippling.

posterior) of the ipsilateral AON (Fig. 2A), and lighter fields were present in the contralateral pars dorsalis and pars lateralis.

A terminal field was also present in the ispsilateral ventral pallidum. Labeled fibers were observed to course caudally in the medial forebrain bundle from the application site to the level of the body of the anterior commissure, where many of the fibers broke into a dense terminal field in the medial ventral pallidum (Fig. 2E,F). The remainder of the fibers entered the medial portion of the cerebral peduncle, in which they could be traced caudally as far as the level of the mammillary bodies. These fibers apparently contributed to an ipsilateral terminal field in the medial substantia nigra, pars reticulata (Fig. 2M). This field was considerably less dense than those observed in the ventral pallidum or anterior olfactory nucleus.

Rostrolateral olfactory tubercle

Experiment 795 is an example of an HRP application in the lateral third of the olfactory tubercle, at a rostrocaudal level similar to that of brain 791 (Figs. 1B; 3C,D).

As in brain 791 in which HRP was deposited in the rostromedial tubercle (Fig. 1A), the AON and MOB were only sparsely labeled. In this case, HRP-containing cells in the AON were confined to the pars lateralis.

Cortical labeling in this brain differed from that observed in experiment 791 in that no labeling was observed in the orbital cortex, perirhinal cortex, or entorhinal area TR. Also, fewer HRP-filled neurons were present in the ventral agranular insular (Fig. 3B,C), and posterior agranular insular cortices (Fig. 3E–H), and in entorhinal areas 28L and 28L′ (Fig. 3K–N). Only in the primary olfactory cortex (Fig. 3B–J) was the amount of labeling comparable to that resulting from retrograde transport from the medial rostral tubercle (brain 791). However, in this brain, the majority of HRP-filled neurons in the olfactory cortex were found rostral to the level of the NLOT, rather than caudal. As in brain 791, labeling in the rostral olfactory cortex was largely restricted to lamina II, while caudally, significant labeling was also present in lamina III.

In the amygdaloid complex, HRP-filled neurons were present in only the anterior division of the basolateral nucleus, the posterolateral cortical nucleus, and bilaterally in the NLOT (Fig. 3G–I). Labeling in the basolateral and cortical nuclei was much lighter than that produced by the rostromedial application in brain 791, while that in the NLOT was similar in these two experiments.

In the thalamus of this brain, HRP was found within cells in nucleus parataenialis (Fig. 3G), nucleus reuniens (Fig. 3H), and nucleus parafascicularis (Fig. 3I). As in the cortex and amygdala, fewer neurons containing HRP were present in these areas than in brain 791.

The pattern of labeling in the brainstem in this experiment was similar to that observed after the rostromedial HRP application in experiment 791, except that labeling was lighter in the ventral tegmental area, and a few neurons in the medial substantia nigra, pars compacta (Fig. 3K,L), contained reaction product.

Terminal fields were observed in this experiment in the AON (Fig. 3A) as described for brain 791, and in the lateral ventral pallidum (Fig. 3E,F). A terminal field was not present in the substantia nigra of this brain.

Intermediate rostral olfactory tubercle

Comparison of Figures 2 and 3 shows that efferents to the rostral olfactory tubercle from the cortex, amygdala, thalamus, and ventral tegmental area primarily terminate medially within the rostral tubercle, while projections from the AON, NLOT, and dorsal raphe (and the MOB) terminate throughout the rostral tubercle. This suggests that there is a medial-lateral gradient in the density of these projections to the rostral tubercle. Evidence that this is indeed the case is provided by experiment 794. In this experiment, HRP was deposited in the portion of the rostral tubercle (Fig. 1B), lying between the areas of the medial application in brain 791 (Fig. 1A) and lateral application in brain 795 (Fig. 1C).

The locations of labeled neurons in the MOB, AON, NLOT, and dorsal raphe, and in all cortical areas but the orbital cortex, which was not labeled, were similar to those observed after an HRP application in the medial rostral olfactory tubercle (brain 791). However, with the exception of the olfactory cortex, the number of labeled neurons in the cortical areas projecting to the olfactory tubercle was substantially less in this brain. On the other hand, labeling in those cortical areas demonstrated in experiment 795 (Fig. 3) to also project to the lateral tubercle, was greater in this experiment than in 795, in which HRP was deposited in the lateral tubercle. Only the

olfactory cortex was much more heavily labeled by retrograde transport from the intermediate tubercle than from either the medial or lateral tubercle.

A similar pattern was observed in the amygdala, thalamus, and ventral tegmental area; labeling in these areas was lighter in this experiment than when HRP was applied in the medial olfactory tubercle (brain 791), but greater than that produced by an application in the lateral tubercle (brain 795).

Terminal fields like those described earlier were present in the AON in this brain. A terminal field was also observed in the ventral pallidum, located lateral to that observed after the medial application in brain 791, but medial to that labeled by the lateral application in brain 795.

Caudal olfactory tubercle

A medial-lateral gradient was observed in the cortical, amygdaloid, thalamic, and ventral tegmental projections to the caudal olfactory tubercle, as well as to the rostral tubercle. There is also a rostral-caudal component to the topography of certain of these projections. Two experiments illustrating these points will be briefly described.

In experiment 792, an iontophoretic application of HRP was placed in the medial caudal tubercle (Fig. 1D). The distribution of labeling observed in this experiment was the same as that seen after HRP was deposited in the medial rostral tubercle (brain 791), with the exception of the AON. As in brain 791, the pars medialis of the AON contained HRP-filled cells, but the pars lateralis and pars ventralis did not. In addition, however, HRP was present in cells of the AON pars posterior in this brain. The number of labeled cells in the thalamus, NLOT, and dorsal raphe in this experiment was similar to that resulting from the rostromedial application in brain 791. However, fewer HRP-containing neurons were present in the amygdala, cerebral cortex, and ventral tegmental area. Terminal fields in this brain were similar to those described for experiment 791.

Experiment 7716 is an example of an HRP application in the intermediate portion of the caudal olfactory tubercle (Fig. 1E). With the exception of the AON, areas labeled in brain 794, the rostral counterpart of this experiment, were labeled here as well. The AON labeling was similar to that observed after a caudal medial application (brain 792); the AON pars medialis and posterior contained HRP filled neurons, but the pars ventralis and lateralis did not. Similar numbers of cells were labeled in the NLOT, thalamus, and dorsal raphe by the caudal intermediate application in this experiment, and by the rostral intermediate application in experiment 794. The cerebral cortex, amygdala, and ventral tegmental area were less heavily labeled in this brain. Terminal fields in the AON and ventral pallidum were similar to those described for brain 794.

These results demonstrate that the cortical, amygdaloid, and ventral tegmental area afferents of the olfactory tubercle terminate more heavily in the rostral that the caudal tubercle. Furthermore, comparison of the pattern of labeling observed in the two brains in which HRP was deposited in the caudal olfactory tubercle (brains 792 and 7716), suggests that the medial-lateral topography noted in the cortical, amygdaloid, thalamic, and ventral tegmental area efferents to the rostral tubercle, also exists in these projections to the caudal tubercle.

Contralateral labeling

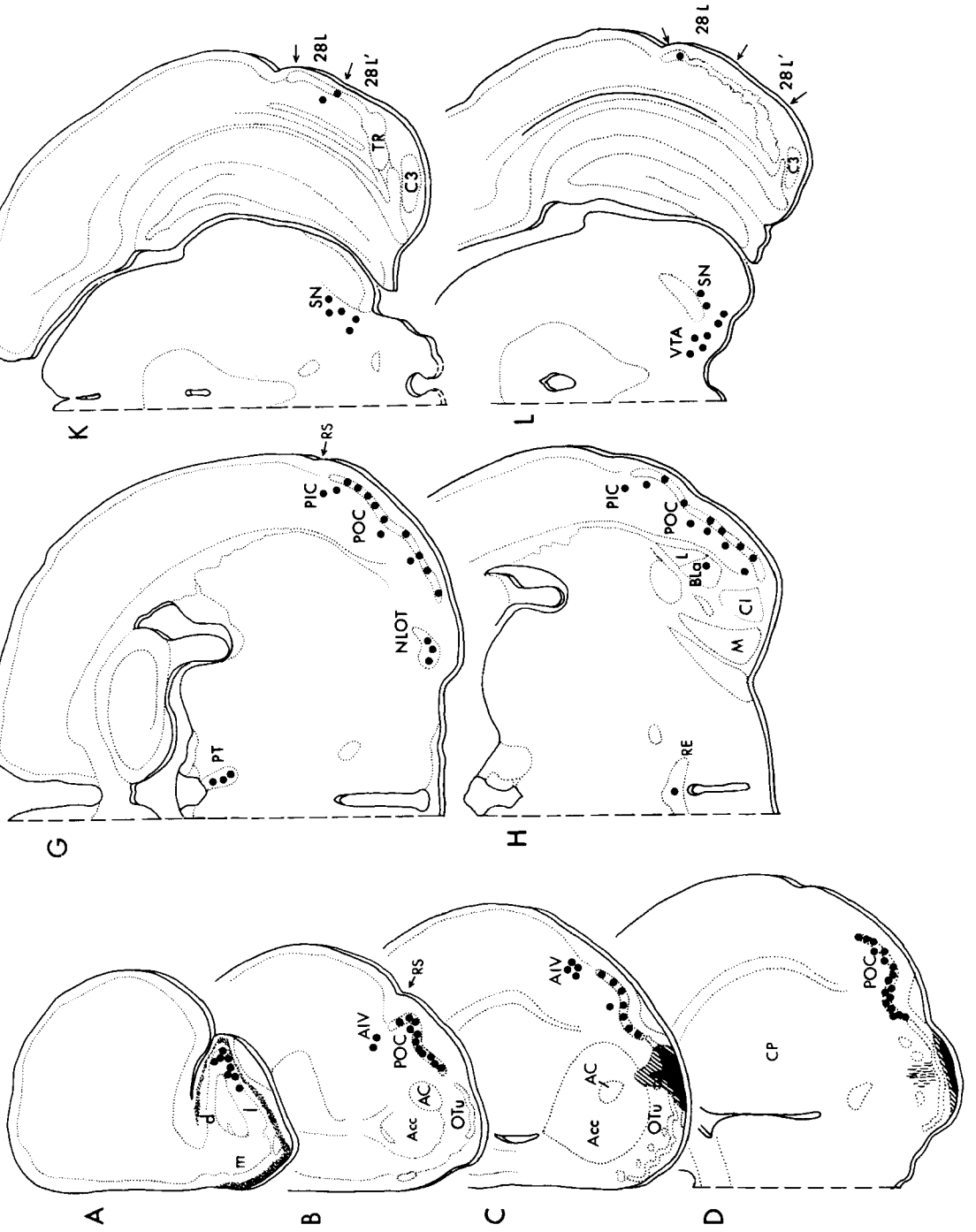
In addition to the ipsilateral labeling described above, small numbers of contralateral HRP-containing cells were observed in various brains in one or more of the ipsilaterally labeled cortical areas, and in the basolateral amygdaloid nucleus.

Labeling in other areas

Areas in which occasional labeled neurons were observed include the posteromedial cortical nucleus of the amygdala, the magnocellular preoptic area, the diagonal band nuclei, the medial and lateral preoptic areas, and thalamic nuclei rhomboidalis, anteromedialis, and dorsomedialis. The results of the control experiments described below suggest that labeling in these thalamic nuclei may have been due to cortical contamination. However, sparse projections to the olfactory tubercle from these nuclei and from the other areas mentioned above cannot be ruled out.

A few labeled cells were also observed in a number of brains adjacent to the needle or pipette tract in the anterior cingulate or infralimbic cortices. These neurons were most likely labeled by direct uptake of HRP drawn into the cortex along the needle or pipette.

Finally, numerous labeled cells were found among the fibers of the terminal field in the ventral pallidum in all the brains described above. However, these cells were so densely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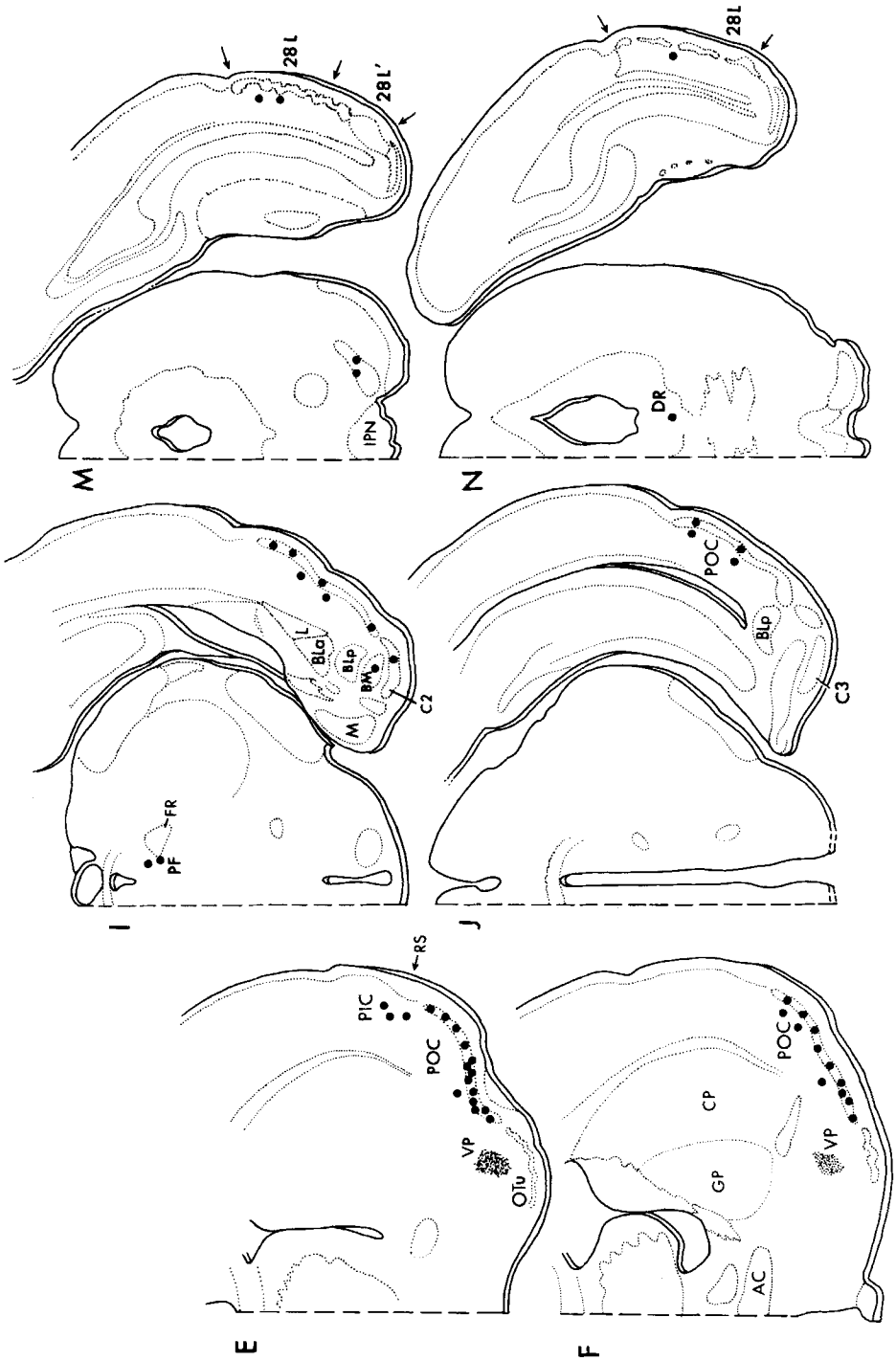
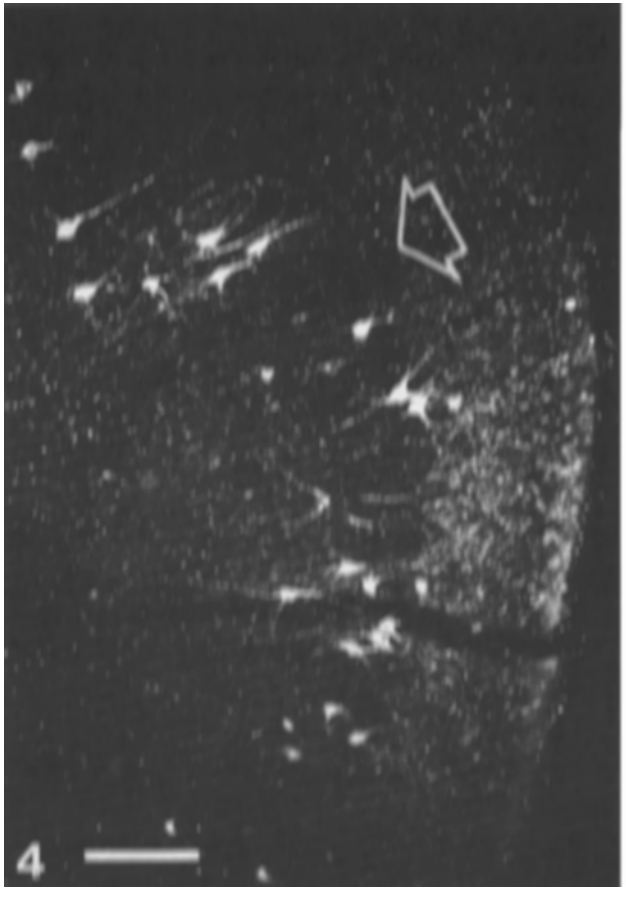


Fig. 3. Series of drawings of representative coronal sections illustrating the distribution of labeled cells and axon terminals in brain 795.



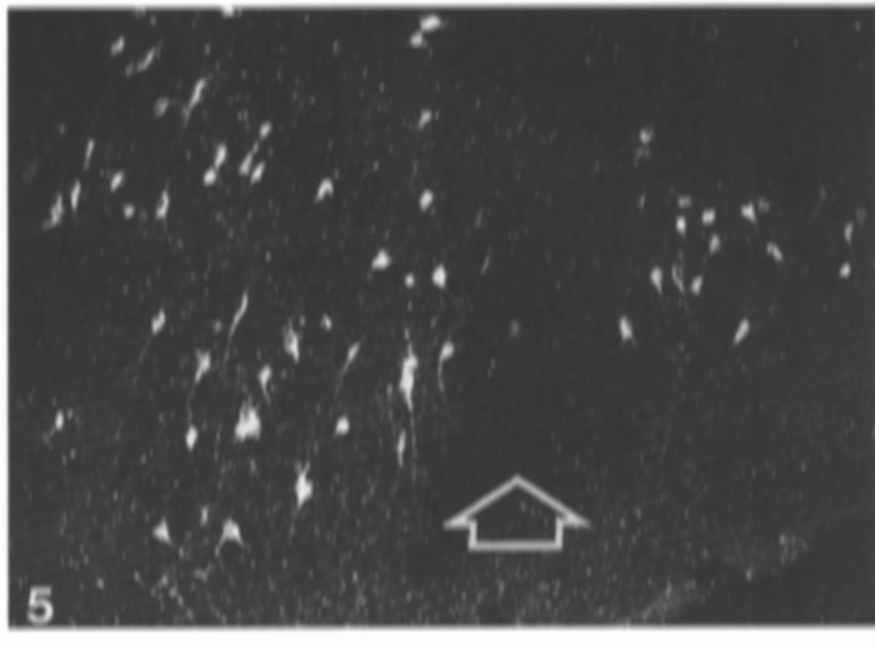


Fig. 4 Darkfield photomicrograph of a coronal section of brain 791 showing labeled pyramidal cells in the posterior agranular insular cortex (above arrow) and primary olfactory cortex (below arrow). Photograph corresponds to the area enclosed by the rectangle in Figure 2I. Calibration bar, 100 μm in Figures 4–6.

Fig. 5. Darkfield photomicrograph of a coronal section of brain 791 showing HRP-containing pyramidal cells in entorhinal areas TR (to left of arrow) and 28L′ (to right of arrow). Photograph corresponds to the area enclosed by the rectangle in Figure 2M.

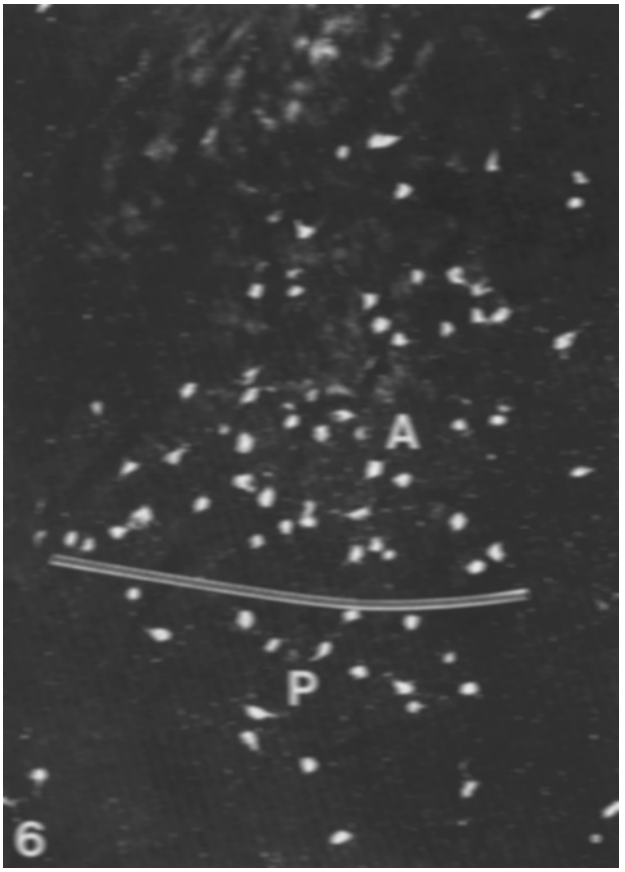


Fig. 6. Darkfield photomicrograph of a coronal section of brain 791, showing labeled neurons in the anterior (A) and posterior (P) divisions of the basolateral nucleus. Photograph corresponds to the area enclosed by the rectangle in Figure 2J.

filled with reaction product that it was felt that their axons had been damaged by the pipette, allowing HRP to enter them by diffusion. While cells in this area may indeed be efferent to the olfactory tubercle, it seems more likely that these neurons project past the tubercle to more rostral regions such as the AON (Haberly and Price, '78a), MOB (de Olmos, et al., '78), or frontal cortex (Heimer, '78).

Control experiments

In the experiments presented in this paper, only small amounts of HRP were drawn from the application site into the cortex dorsal to the olfactory tubercle as the micropipette was withdrawn from the brain. However, since several of the areas described above, in which labeled cells were found, are known to project to the cortical areas traversed by the micropipette (Jones and Leavitt, '74; Beckstead, '76; Krettek and Price, '77b), in one experiment (7716, Fig. 1F), the micropipette was introduced into the tubercle at an angle from the opposite side of the brain to avoid contaminating the cortex dorsal to the tubercle, and in several brains small applications of HRP were made in the cortex overlying the tubercle. The amount of HRP deposited in the cortex of the latter brains was much greater than that present in the cortex of the experimental brains.

Areas containing labeled cells in the experimental brains and in the control brains in which HRP was deposited in the frontal cortex included the paraventricular thalamic nucleus and the dorsal raphe. Labeling in these two areas after injection of HRP directly into the

frontal cortex was quantitatively similar to that produced by HRP applications in the tubercle, in which only minimal amounts of HRP were deposited in the cortex. Therefore, these nuclei must project to the olfactory tubercle as well as to the frontal cortex.

DISCUSSION

Technical considerations

The HRP technique has several qualifications which must be considered when interpreting data obtained by the use of this method. These include the possibility that not all neurons may be capable of transporting HRP, transport by fibers-of-passage, and the difficulty in precisely defining the effective size of an HRP application site. These matters and others relating to the use of the HRP technique have been discussed in the first paper in this series (Newman and Winans, this issue.

Afferent connections of the olfactory tubercle

Previously unreported projections to the olfactory tubercle identified in the present study include those from the parataenial thalamic nucleus, the posterior agranular insular cortex, and perirhinal cortex. In addition, contralateral labeling was observed in various brains in these cortical areas, as well as in the entorhinal and primary olfactory cortices, and the basolateral amygdaloid nucleus. These contralateral projections to the olfactory tubercle are consistent with the findings of van Alphen ('69) and de Olmos and Ingram ('72), and are similar to the results observed in our study of the afferents of nucleus accumbens (Newman and Winans, this issue).

Although the afferent connections of the olfactory tubercle and their topography have never been systematically examined prior to this study in the hamster, many of the connections described here have been reported in anterograde tracing experiments in various species. The olfactory tubercle has been shown to receive fibers from both the MOB and AON (Price, '73; Scalia and Winans, '75; Broadwell, '75a,b; Devor, '76; Rosene and Heimer, '77; Haberly and Price, '78a,b), but in the present study, the MOB was only very lightly labeled by HRP applications in the olfactory tubercle, despite the tubercle's reputation as an important olfactory center. The AON also contained only occasional labeled neurons. Portions of the AON efferent to the tubercle include the medial, lateral, ventral, and posterior subdivisions. When differences in nomencature are taken into account, these findings are in agreement with the results of Haberly and Price ('78) for the caudal olfactory tubercle of rat, except that in the hamster, no HRP-containing neurons were observed in the area of the "dorsal peduncular cortex" of Haberly and Price.

In agreement with the results of this study, the olfactory cortex (Heimer, '72; de Olmos, '72; Price, '73; Haberly and Price, '78a) and entorhinal cortex (Haberly and Price, '78a) have been reported to project to the olfactory tubercle in the rat. In the hamster, the projections to the whole of the tubercle from the anterior part of the olfactory cortex were found to be primarily from pyramidal cells in cortical lamina II, while efferents from more posterior regions of the olfactory cortex arise in lamina III as well, as described by Haberly and Price ('78a) for the rat caudal tubercle.

Brainstem nuclei known to project to the olfactory tubercle of the rat include the substantia nigra and ventral tegmental area (Ungerstedt, '71; Björklund and Lindvall, '78; Fallon and Moore, '78), and the dorsal and medial raphe nuclei (Bobillier et al., '76). In the hamster, ventral mesencephalic efferents to the tubercle are largely from the ventral tegmental area; only a few labeled neurons were ever observed in the substantia nigra. In partial agreement with the findings of Bobillier et al. ('76) in the cat, the dorsal raphe, but not the medial raphe, was found to project to the olfactory tubercle of the hamster. Species variation may account for this discrepancy.

Other areas previously reported to project to the olfactory tubercle, which were also observed to do so here, include the rostral sulcal cortex (Leonard, '69; Beckstead, '79), the anterior and posterolateral cortical, basolateral, and basomedial amygdaloid nuclei (Krettek and Price, '78a; Haberly and Price, '78a), the NLOT (Haberly and Price, '78a), and the paraventricular, parafascicular, and reuniens thalamic nuclei (Haberly and Price, '78a; Herkenham, '78).

Although new connections were identified for the olfactory tubercle and several previously described connections were confirmed in this study, some previously reported projections to the olfactory tubercle were not found in the hamster. Leonard ('69) and Beckstead ('79), using anterograde techniques in the rat, found the medial frontal cortex to be efferent to the olfactory tubercle. Although only occasional HRP-containing neurons were observed here in the medial cortex of the hamster,

projections from these cortical areas cannot be ruled out. The degeneration observed by Leonard ('69) was in lamina III of the tubercle, but the HRP applications in the experiments described here were centered in laminae I and II. Therefore, the medial cortex may have been only lightly labeled by the relatively low HRP concentration of lamina III.

Johnson ('65), Raisman ('66), and Siegel and Tassoni ('71b), using degeneration methods, have suggested that the septum is efferent to the olfactory tubercle, and Siegel and Tassoni ('71a), de Olmos and Ingram ('72), and Siegel et al. ('75) have observed degeneration in the olfactory tubercle after placing lesions in the hippocampus. In the present study, no labeling was present in these areas after HRP applications in the tubercle. It is probable that the degenerating fibers observed by the above investigators were entorhinal efferents passing to the tubercle in the fimbria or fornix, which were interrupted by hippocampal or septal lesions. This interpretation is in agreement with the autoradiographic experiments of Swanson and Cowan ('77, '79).

Fallon et al. ('78), using the HRP method, have reported the islands of Calleja in the rat to be reciprocally connected with the septum and the nucleus accumbens. However, their HRP injections were quite large, and it is probable that the labeling they observed in the tubercle resulted from diffusion of HRP from the injection sites. Figure 13B in their paper strongly suggests that this is true in the case of the septum.

Efferent connections of the olfactory tubercle

In agreement with the results of the present study, Swanson ('76) has reported that the olfactory tubercle projects to the AON and substantia nigra of the rat. A number of other efferents which have been reported to arise in the olfactory tubercle, however, were not confirmed here, probably because of differences in the laminae of the tubercle involved in the various studies. Dennis and Kerr ('76) have reported that efferents from the olfactory tubercle innervate the main olfactory bulb of the rat. This connection was not noted in the present study or by other investigators (Broadwell and Jacobwitz, '76; Haberly and Price, '78a,b; Davis et al., '78). However, de Olmos et al. ('78) have recently shown cells deep to lamina III of the tubercle to project to the rat's olfactory bulb, and have suggested that the question of whether tubercular cells project to the bulb, is a problem of definition: if cells deep to lamina III are considered to belong to the olfactory tubercle, then the tubercle may indeed be efferent to the bulb. This connection may therefore not have been demonstrated in the experiments presented here, since the concentration of HRP deep to lamina III was certainly too low for anterograde transport to occur from this area.

Projections from the olfactory tubercle of the rat have been described to the dorsomedial thalamic nucleus, the nuclei gemini of the hypothalamus, and the ventral pallidum, (Scott and Leonard, '71; Heimer et al., '75). Only the projection to the ventral pallidum was observed in the present study. However, the efferents to the nuclei gemini and dorsomedial nucleus have been shown to originate in cells of lamina III of the tubercle (Scott and Chafin, '75; Heimer et al., '75; Siegel et al., '77). These connections may not have been demonstrated in the preset study because the HRP applications usually involved the full thickness of laminae I and II, but only the superficial part of lamina III.

Fallon et al. ('78) have reported the olfactory tubercle to be efferent to the septum, nucleus accumbens, and the amygdala. However, their evidence for these conclusions is not altogether convincing, since their HRP applications were quite large. Terminal fields were not observed in these areas in the present study.

Topographical organization of the connections of the olfactory tubercle

Evidence has been obtained in a number of species that the main olfactory bulb projections to the olfactory tubercle may be topographically organized (Price, '73; Devor, '76; Rosene and Heimer, '77; Scott and McBride, '78). The results of this study show that tubercular afferents from a variety of other areas are also topographically arranged.

The pattern of labeling observed in the AON in the experiments described above may be summarized as follows: The pars medalis of the AON projects to all but the rostrolateral portion of the tubercle; the pars posterior was labeled only in brains in which HRP was deposited in the caudal tubercle; the pars lateralis projects to all parts of the rostral tubercle, while the pars ventralis was labeled only after HRP applications in the medial and intermediate rostral tubercle; labeling was never observed in the pars dorsalis or externa.

Cortical projections to the olfactory tubercle are topographically arranged with respect to both the medial-lateral and rostral-caudal axes of the tubercle. In an experiment in which HRP was deposited in the rostromedial tubercle (brain 791; Fig. 2), the amount of labeling in all labeled cortical areas (orbital, ventral agranular insular, posterior agranular insular, perirhinal, and enthorhinal cortices), with the exception of the olfactory cortex, was much greater than that produced by an HRP application in the rostrolateral tubercle (case 795; Fig. 3), while labeling after HRP applications in the intermediate tubercle (brain 794) was intermediate in density. The olfactory cortex, on the other hand, was more heavily labeled by retrograde transport of HRP from the intermediate tubercle than from either medial or lateral tubercular areas. This medial-lateral pattern is also apparent in brains having HRP applications in the caudal tubercle (brains 792 and 7716).

A rostral-caudal component is also evident in the topography of the projections of the primary olfactory, entorhinal, and posterior insular cortices; these areas contained many more labeled cells in the brains having rostral HRP applications (experiments 791, 794, and 795) than in brains which had caudal applications (experiments 792 and 7716). This rostral-caudal topography is less-marked in the projections of the other labeled cortical areas.

The primary olfactory cortical efferents display point-to-point topography, in contrast to the projections of the other cortical areas, which are topographic only with respect to their termination within the tubercle. The olfactory cortex caudal to the NLOT projects primarily to the rostromedial tubercle (brain 791; Fig. 2), while the cortex rostral to NLOT projects most heavily to the rostrolateral tubercle (brain 795, Fig. 3). In brain 794, in which the HRP application site was centered in the intermediate part of the rostral tubercle, an intermediate level of the primary olfactory cortex, overlapping the level of the NLOT, was labeled most densely. Thus, successively more rostral olfactory cortical areas project most heavily to correspondingly more lateral tubercular areas. This same pattern was seen in experiments in which HRP applications were made in the medial (brain 792) and intermediate (brain 7716) caudal olfactory tubercle.

The amygdaloid projections to the olfactory tubercle, like the cortical projections, display a topography having both medial-lateral and rostral-caudal components. The anterior cortical, basomedial, and posterior basolateral nuclei were observed to contain labeled neurons only when HRP was deposited in the medial portion of the rostral or caudal tubercle (brains 791 and 792). The anterior basolateral and posterolateral cortical nuclei were labeled both in these medial tubercle experiments and in experiments in which HRP applications were made in more lateral areas of the rostral (brains 794 and 795) or caudal (brain 7716) tubercle. However, the amount of labeling in these latter nuclei decreased progressively as the application site became increasingly more lateral.

A less-marked rostral-caudal topography is present in the amygdaloid efferents, particularly those from the basolateral nucleus. Both divisions of the basolateral nucleus were labeled more heavily after an HRP application in the rostromedial tubercle (brain 791) than in brain 792, in which HRP was applied in the caudomedial tubercle. A similar, though less-marked pattern of labeling was observed in the cortical nuclei. The NLOT efferents were distributed evenly throughout the olfactory tubercle of the hamster.

The topographical organization of the amygdaloid afferents described above is in poor agreement with the results of earlier studies. Krettek and Price ('78a) have reported the anterior division of the basolateral nucleus of the rat and cat to project laterally within the tubercle, and the posterior division to project medially. Haberly and Price ('78a) reported that the projection from the rat NLOT was directed primarily to the lateral tubercle, and did not find that fibers from the anterior and posterolateral cortical nuclei terminate topographically within the tubercle as reported here. Since the topographical characteristics observed here in the hamster are quite pronounced, especially the medial-lateral component, species variation appears to be a likely explanation for these discrepancies.

The tubercular projections from the thalamus are mainly to the medial olfactory tubercle. Labeling in the thalamus decreased successively in brains in which HRP was deposited in the medial, intermediate, and lateral portions of the rostral tubercle (brains 791, 794, and 795). This pattern was also seen in the caudal olfactory tubercle (experiment 792 and 7716). A rostral-caudal component to the topography of these efferents was not observed. With the exception of that from nucleus parafascicularis, the thalamic projec-

tions to the tubercle are topographic only in their termination within the tubercle; they appear to arise in all parts of their respective nuclei. Efferents from parafascicularis, however, are largely from cells in the rostral portions of the nucleus only, ventromedial to the fasciculus retroflexus.

The ventral tegmental area (VTA), like the cerebral cortex, thalamus, and amygdala, projects most heavily to the medial olfactory tubercle. Labeling in this area was greater in brains having medial HRP applications (brains 791 and 792) than in brains in which HRP was deposited in more lateral parts of the rostral or caudal tubercle (brains 795 and 7716). There is also a rostral-caudal component to this topography; labeling in the VTA was heavier in experiments in which HRP was deposited in the rostral olfactory tubercle (brains 791, 794, and 795) than in brains having caudal applications (brains 792 and 7716). Fallon et al. ('78) have reported that cells of the VTA of the rat project to the medial tubercle, while the lateral tubercle is innervated by neurons in the lateral VTA and medial substantia nigra. In the hamster, only a few labeled neurons were present in the nigra after HRP applications in the lateral tubercle; the ventral mesencephalic projection to the lateral as well as medial tubercle was primarily from the VTA. Apparently the topographic organization of the brainstem dopaminergic nuclei differs between these species.

Of the efferent projections of the olfactory tubercle, only that to the ventral pallidum was found to display topographical organization in the present study. Medial tubercular areas project to the medial ventral pallidum (brains 791, 792), lateral areas to the lateral ventral pallidum (brain 795), and intermediate areas (brains 794 and 7716) to intermediate regions of the ventral pallidum. A rostral-caudal component to the topography of this projection was not evident, though this could not be determined with certainty without the aid of brains sectioned in the saggital or horizontal planes.

The substantia nigra was found to contain a terminal field only in brains having HRP applications in the medial olfactory tubercle (experiments 791 and 792). However, this terminal labeling was rather faint, and it is possible that slight differences in the processing of brains having lateral HRP applications might have rendered equally faint nigral fields undetectable. In particular, terminal labeling seems prone to fading caused by overexposure of brain sections to ethanol during dehydration. Therefore, projections from the lateral tubercle to the nigra cannot be ruled out.

Evidence supporting the ventral striatal concept

In recent years it has become apparent that the limbic and striatal systems are not as anatomically isolated from each other as was once believed. Heimer and Wilson ('75) and Heimer ('78) have proposed that the nucleus accumbens, olfactory tubercle, substriatal gray (the portion of the caudatoputamen ventral to the posterior limb of the anterior commissure), and the cell bridges connecting these areas, together referred to as the "ventral striatum," are functionally related striatal structures which collectively provide a means through which the allocortical components of the limbic system may influence the striatum. The results of the present study on the connections of the olfactory tubercle and of the first study in this series on the connections of the nucleus accumbens (Newman and Winans, this issue) support these ideas.

Both the olfactory tubercle and nucleus accumbens were found to receive afferents from areas which project to the caudatoputamen, including the cerebral cortex, intralaminar thalamus, and the dopaminergic brainstem nuclei. Examination of the organization of the cortical projections to the ventral striatum reveals a number of parallels in the cortical connections of the dorsal and ventral striatal areas. The basic arrangement of neocortical afferents to the dorsal striatum is such that cortical areas project most strongly to the portions of the caudatoputamen lying closest to them (Kemp and Powell, '70). The cortical efferents to the ventral striatum also follow this pattern; they arise in cortex lying in, and ventral to, the rhinal sulcus, and terminate in the most ventral part of the striatum—the ventral striatum proper. Thus, the whole of the cortical afferents to the corpus striatum is seen to form a continuum. Furthermore, this pattern is observed in the projections of individual cortical areas to the ventral striatum. For example, dorsal (rostral) subicular areas project to rostral nucleus accumbens, while ventral (caudal) subicular efferents innervate only caudal nucleus accumbens. Similarly, entorhinal area 28L projects only to the lateral portion of caudal accumbens, while fibers from the more medial areas 28L′ and TR terminate in the medial portion of caudal accumbens.

The thalamic connections of the ventral striatum also reflect the continuity of the dorsal and ventral striatal areas. Whereas the projections from the caudal intralaminar nucleus parafascicularis to nucleus accumbens and the olfactory tubercle arise from cells lying ventromedial to the fasciculus retroflexus, Nauta et al. ('74) and Kuypers et al. ('74) have presented data from the rat that the majority of parafascicular neurons projecting to the caudatoputamen lie in the portion of nucleus parafascicularis dorsolateral to the fasciculus retroflexus. A similar example is provided by the finding of this study that the rostral intralaminar thalamic projection to the ventral striatum is largely from centralis medialis, the most medial of the rostral intralaminar nuclei, together with the observation of Jones and Leavitt ('74) that the medial rostral intralaminar nuclei project to ventral regions of the caudate nucleus, while more lateral areas project to dorsal parts of the caudate. These relationships provide support for the belief that the caudatoputamen, nucleus accumbens, and the olfactory tubercle are related striatal structures, since the intralaminar nuclei are thus seen to project topographically to the whole of the corpus striatum.

In addition to the intralaminar thalamic projections to accumbens and the tubercle, the ventral striatum receives input from the midline thalamic nuclei parataenialis, paraventricularis, and reuniens. Of these, only the connections of reuniens in the rat have been thoroughly studied (Herkenham, '78). The efferent connections of reuniens are primarily to those limbic cortical areas which are themselves efferent to the ventral striatum. Perhaps the midline nuclei function in the ventral striatal system in a manner analogous to the ventral tier nuclei of the dorsal system, providing a means by which ventral striatum can interact reciprocally with cortical areas efferent to it.

The ventral striatum, like the caudatoputamen, receives dopaminergic afferents from the ventral midbrain, and the topography of this projection to nucleus accumbens and the olfactory tubercle is complementary to that to the dorsal striatum. In the present study, cells in all parts of the ventral tegmental area were found to be efferent to both nucleus accumbens and the olfactory tubercle, and in addition, the lateral portion of the tubercle was shown to receive a small projection from the medial substantia nigra. The dopaminergic efferents to the dorsal striatum, in contrast, are known to arise from the lateral as well as medial substantia nigra, but only from the lateral portion of the ventral tegmental area (Fallon and Moore, '78). This projection, then, like those from the cortex and intralaminar thalamus, is topographically continuous over the whole of the striatum.

The efferents of the ventral striatum, like the afferent connections discussed above, reflect the continuity of the dorsal and ventral striatal areas. The projections of the whole of the striatum to the pallidum are topographically arranged such that the dorsal striatum projects to dorsal pallidal areas, while efferents from the ventral striatum innervate ventral regions of the globus pallidus (i.e., the ventral pallidum). Furthermore, efferents from the nucleus accumbens, which lies dorsal to the olfactory tubercle, terminate in the ventral pallidum dorsal to the efferents from the tubercle.

The ventral striatum and the limbic system

The ventral striatum is one of the few brain areas in which the limbic and striatal systems interact directly. In addition to the cortical, thalamic, and ventral mesencephalic afferents it receives in common with the dorsal striatum, the ventral striatum receives projections from a variety of limbic system structures, including the primary olfactory cortex, entorhinal cortex, hippocampus, subiculum, and amygdala. Therefore, it seems likely that an important function of the ventral striatum is the processing of limbic input to the striatal system. More specifically, the fact that a number of the limbic areas which project to the ventral striatum receive multimodal sensory information (Whitlock and Nauta, '56; Kuypers et al., '65; Jones and Powell, '70; Seltzer and Pandya, '74; van Hoesen and Pandya, '75b; Herzog and van Hoesen, '76), suggests that the ventral striatum, like the dorsal striatum, coordinates motor system activity with somatic sensory input. However, the ventral striatum is also involved in the control of visceral function (Koikegami et al., '67; Smith and Holland, '75), and receives direct and indirect visceral sensory information (Scalia and Winans, '75; van Hoesen and Pandya, '75a; Norgren '76; Rosene and Heimer, '77). It is likely, then, that the ventral striatum, rather than being exclusively concerned with somatic motor control, is involved with integrating limbic system information into visceral as well as somatic effector systems, including

hormone-secreting cells of the hypothalamus and pituitary, and lower motor neurons of the brainstem and spinal cord.

Further study of the anatomy of the ventral striatal system will be required to evaluate this hypothesis. Since the ventral pallidum is the recipient of the major efferent projection of the ventral striatum, determination of the connections of the ventral pallidum should help to clarify the functions of the ventral striatal system.

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